**Revised in December 2022 (5th edition)

**Revised in March 2022 (4th edition, changes in efficacy and usage)

Storage method: 2-8ÿ Storage

period: 4 years

Japanese standard product classification number
874291

抗HER2[注1)] ヒト化モノクローナル抗体　抗悪性腫瘍剤

トラスツズマブ（遺伝子組換え）製剤

生物由来製品、処方箋医薬品[注2)]

	60 for injection	150 for injection
Approval number	21600AMY00065	21300AMY00128
Sales start	August 2004	June 2001

ハーセプチン®注射用60
ハーセプチン®注射用150
HERCEPTIN® for Intravenous Infusion

ÿ1ÿHER2ÿHuman Epidermal Growth Factor Receptor Type 2 (human epidermal growth factor receptor type 2, also known as c-erbB-2)

Note 2) Caution: Use with prescription from a doctor, etc.

CHUGAI

Roche ロシュ グループ

1. Warning

1.1 Cancer chemotherapy containing this drug should only be administered at a medical facility that can adequately respond to emergencies, under the supervision of a doctor with sufficient knowledge and experience in cancer chemotherapy, if this drug is deemed appropriate. It should be carried out only for cases. In addition, before starting treatment, the effectiveness and risks should be fully explained to the patient or his or her family, and consent should be obtained before administration.

1.2 There have been reports of serious cardiac disorders such as heart failure, leading to death, so be sure to check the patient's cardiac function before starting administration of this drug. In addition, during administration of this drug, cardiac function tests (e.g., echocardiography) should be performed as appropriate, and the patient's condition (including changes in left ventricular ejection fraction (LVEF)) should be carefully monitored. In particular, cardiac function tests (e.g. echocardiography) should be performed frequently for the following patients: [See 8.1, 9.1.1-9.1.7, 11.1.1]•Patients receiving anthracycline drugs or a history of previous treatment patient with

•Patients receiving radiation to the chest•Patients with symptoms of heart failure•Patients with coronary artery disease (myocardial infarction, angina pectoris, etc.) or their past history a patient

•Patients with hypertension or a history of hypertension

1.3 Among the infusion reactions that often occur during administration of this drug or within 24 hours after starting administration of this drug, serious side effects such as anaphylaxis and lung damage (bronchospasm, severe hypotension, acute respiratory distress syndrome, etc.) occur. Cases leading to death have been reported. These side effects are particularly likely to become severe in patients with or a history of difficulty breathing at rest (due to lung metastases, cardiovascular disease, etc.), so they should be administered carefully while closely monitoring the patient's condition. To administer. [See 9.1.8, 11.1.2, 11.1.3]

2. Contraindications (Do not administer to the following patients)

Patients with a history of hypersensitivity to the components of this drug

3. Composition and properties 3.1 Composition

Brand name	Herceptin Injection 60	Herceptin Injection 150
Active ingredient	In 1 vial In 1 vial Trastuzumab (genetical recombination) Note) Trastuzumab (genetical recombination) Note) 60mg 150mg In 1 vial In 1 vial Trehalose hydrate 54.48mg Trehalose hydrate 136.2mg L-Histidine	
Additive	hydrochloride hydrate 1.34 mg L-histidine hydrochloride hydrate 3.36mg L-histidine 0.86mg L-histidine 2.16mg Polysorbate 20 0.24mg Polysorbate 20 0.6mg Note) This drug is manufactured using Chinese hamster ovary cells. Pig-derived ingredients (peptone) are used as culture medium components in the manufacturing process.	

ing.

preparation Properties of the

Brand name	Herceptin Injection 60	Herceptin Injection 150 Injection (vial) White to
Dosage form Properties	slightly yellow lump	

Osmolality ratio (ratio to physiological saline)	1.0 (after preparation with JP water for injection and JP physiological saline)
The properties after dissolving in JP Water for Injection are as follows.	
solution	It is a clear or slightly opalescent colorless to slightly yellow liquid.
pH	5.8ÿ6.4
Osmolarity	55ÿ70mOsm/kg

ÿ **4. Efficacy or effect**

•Breast cancer with confirmed HER2 overexpression •Unresectable advanced/recurrent gastric cancer with HER2 overexpression •HER2-positive advanced/recurrent salivary gland cancer that cannot be completely resected •HER2-positive disease that has worsened after cancer chemotherapy Advanced or recurrent colorectal cancer that cannot be cured

5. Precautions related to efficacy or efficacy (Breast cancer with confirmed HER2 overexpression) 5.1 Testing for HER2 overexpression should be performed by a pathologist or testing operator with sufficient experience. Implemented at the facility.

<Advanced/recurrent gastric cancer that is confirmed to have overexpression of HER2 and cannot be resected> 5.2 Testing for HER2 overexpression should be performed by a pathologist with sufficient experience or a testing facility. Implemented at the facility.

5.3 The efficacy and safety of postoperative adjuvant therapy with this drug have not been established.

5.4 Familiarize yourself with the contents of ``17.Clinical results'' regarding the primary site, tissue type, etc. in the junctional region, and select appropriate patients. [See 17.1.10]

<HER2-positive advanced/recurrent salivary gland cancer that cannot be completely resected> 5.5 By examination at a pathologist or laboratory with sufficient experience, Administer to patients confirmed to be HER2 positive. For testing, use approved in vitro diagnostic drugs or medical devices. Information regarding approved in vitro diagnostic drugs or medical devices can be obtained from the following website. https://www.pmda.go.jp/review-services/drug-reviews/review

information/cd/0001.html

ÿUnresectable progression/recurrence of HER2-positive disease that worsened after cancer chemotherapy colorectal cancer>

ÿ **5.6** By examination by a pathologist or laboratory with sufficient experience, Administer to patients confirmed to be HER2 positive. For testing, use approved in vitro diagnostic drugs or medical devices. Information regarding approved in vitro diagnostic drugs or medical devices can be obtained from the following website. https://www.pmda.go.jp/review-services/drug-reviews/review

information/cd/0001.html

ÿ **5.7** RAS The efficacy and safety of this drug in patients who are positive for gene mutations have not been established.

ÿ **5.8** The efficacy and safety of this drug in patients who have not been treated with fluoropyrimidine anti-cancer drugs, oxaliplatin, or irinotecan hydrochloride hydrate have not been established.

ÿ **5.9** The efficacy and safety of postoperative adjuvant therapy with this drug have not been established. **5.10**

ÿ Regarding the prior treatment history of patients enrolled in clinical trials, please be sure to thoroughly understand the contents of section 17. “Clinical Results” and fully understand the efficacy and safety of this drug before proceeding with treatments other than this drug. Careful consideration should be given to the implementation of this therapy and selection of appropriate patients. [See 17.1.12]

ÿ **6. Dosage and dosage**

Method A or Method B is used for breast cancer in which overexpression of HER2 has been confirmed.

Method B is used in combination with other antineoplastic agents for unresectable, advanced, or recurrent gastric cancer in which overexpression of HER2 has been confirmed.

Method B is used in combination with docetaxel for HER2-positive, advanced or recurrent salivary gland cancer that cannot be completely resected. Method

B is used in combination with pertuzumab (genetical recombination) for HER2-positive, unresectable, advanced or recurrent colorectal cancer that has progressed after cancer chemotherapy.

Method A: The usual dose for adults is 4 mg/kg (body weight) of trastuzumab (genetical recombination) once a day for the first dose, and 2 mg/kg (body weight) over 90 minutes for subsequent doses at weekly intervals. Administer intravenously.

Method B: The usual dose for adults is 8 mg/kg (body weight) of trastuzumab (genetical recombination) once a day for the first dose, and 6 mg/kg (body weight) over 90 minutes for subsequent doses every 3 weeks. Administer intravenously. If the first dose is well tolerated, the time for subsequent doses can be shortened to 30 minutes.

7. Precautions related to dosage and administration

(Common indications) 7.1 When administering this drug, if the scheduled administration is delayed for some reason. In case of delay, it is recommended to administer as follows.

7.1.1 If administration is delayed within one week from the scheduled administration date, method A Administer 2mg/kg, and 6mg/kg in method B.

7.1.2 If administering more than 1 week after the scheduled administration date, administer again at the initial dose (4 mg/kg for Method A, 8 mg/kg for Method B). From the next time onward, administer 2 mg/kg at one-week intervals for method A, and administer 6 mg/kg at three-week intervals for method B.

<Breast cancer with confirmed HER2 overexpression> 7.2 Pay attention to the following points regarding postoperative drug therapy. **7.2.1** Efficacy and safety of administration for longer than 1 year have not been established. **7.2.2** This drug should be administered after thoroughly understanding the section ``17.Clinical results''. [See 17.1.9]

<Advanced/recurrent gastric cancer that is confirmed to overexpress HER2 and cannot be cured> 7.3 This drug should be started in combination with other antineoplastic agents. When selecting an anti-cancer agent to be used in combination with this drug, be sure to thoroughly understand the contents of section 17. “Clinical Results.” [See 17.1.10]

8. Important basic precautions

(Common indications) 8.1 Cardiac disorders may occur, so be sure to check the patient's cardiac function before starting administration of this drug. During administration of this drug, cardiac function tests (e.g., echocardiography) should be performed as appropriate depending on the development status and severity of cardiac symptoms, and the patient's condition (including changes in left ventricular ejection fraction (LVEF)) should be carefully monitored. Monitor and decide whether to suspend, restart, or discontinue administration. [See 1.2, 9.1.1-9.1.7, 11.1.1] **8.2** The usefulness of premedication (antihistamines, corticosteroids, etc.) for the purpose of avoiding infusion reactions has not been confirmed. **8.3** Tumor lysis syndrome may occur, so the patient's condition should be carefully monitored, including serum electrolyte concentrations and renal function tests. [See 11.1.9]

8.4 When using this drug, be careful not to confuse it with trastuzumab emtansine and trastuzumab deruxtecan, which have similar generic names.

<Breast cancer with confirmed HER2 overexpression> 8.5 When using this drug for preoperative drug therapy (method A, method B), postoperative drug therapy method A, and method B for metastatic breast cancer, please refer to the relevant literature. (“ Report on Applicability of Publicly Known Applications by the Review Committee for Unapproved and Off-label Drugs with High Medical Needs ” 1)-3) , etc.).

9. Precautions regarding patients with specific backgrounds

9.1 Patients with complications/medical history, etc. 9.1.1 Patients with serious cardiac disorders

Do not administer this drug unless it is judged to be unavoidable for therapeutic reasons. [See 1.2, 8.1, 11.1.1] **9.1.2 Patients with a history of prior treatment with anthracyclines**

Heart disorders such as heart failure are likely to occur. [See 1.2, 8.1, 11.1.1]

9.1.3 Patients receiving radiation to the chest When concurrently administering radiation to the chest, set an appropriate radiation treatment plan and pay attention to the occurrence of cardiac disorders. Heart disorders such as heart failure are likely to occur. [See 1.2, 8.1, 11.1.1] **9.1.4 Patients with or history of heart failure symptoms**

Symptoms may worsen. [See 1.2, 8.1, 11.1.1] **9.1.5 Patients with reduced left ventricular ejection fraction (LVEF), uncontrolled arrhythmias, or clinically significant valvular heart disease symptoms** worsen There is a risk. [See 1.2, 8.1, 11.1.1] **9.1.6 Patients with or past history of coronary artery disease (myocardial infarction, angina pectoris, etc.)**

Certain patient symptoms may worsen. Or, cardiac disorders such as heart failure are likely to occur. [See 1.2, 8.1, 11.1.1]

9.1.7 Patients with hypertension or a history of hypertension are more likely to develop cardiac disorders such as heart failure. [See 1.2, 8.1, 11.1.1] **9.1.8 Patients with dyspnea at rest (due to lung metastasis, cardiovascular disease, etc.) or patients with a history of such**

infusion reactions are more likely to become severe. [See 1.3, 11.1.2, 11.1.3]

9.4 Persons with reproductive potential

Women who may become pregnant should be instructed to use appropriate contraception during treatment with this drug and for at least 7 months after completion of treatment. [See 9.5] **9.5 Pregnant women** or women who may become pregnant should only be administered if the therapeutic benefits are judged to outweigh the risks. There have been reports of oligohydramnios occurring in pregnant women who received this drug. There have also been reports of cases in which oligohydramnios developed, resulting in fetal/neonatal renal failure, fetal growth retardation, neonatal respiratory distress syndrome, fetal lung hypoplasia, etc., which led to death. In animal experiments (monkeys), placental passage (1, 5, 25 mg/kg repeated doses) has been reported4), but no effects on the fetus have been reported . [See 9.4] **9.6 Considering the therapeutic benefits of breastfeeding** and the benefits of breastfeeding, consider continuing or discontinuing

breastfeeding. Although there is no data regarding milk transfer in humans, it has been reported that human IgG transfers into breast milk. In addition, in animal experiments (monkeys), transfer into milk (repeated administration of 25 mg/kg) has been reported5). **9.7** No clinical studies have been conducted in children. 9.8 Care should be taken when administering to elderly **patients,** while monitoring the patient's condition, including

conducting cardiac function, liver/kidney function tests, and blood tests. Physiological

functions decline in the elderly.

10. Interaction 10.2

Precautions for concomitant use (Be careful with

concomitant use) Drug name, etc.	Clinical symptoms/measures	Mechanism/risk factors
risk of heart disorders. Be especially careful as it is a type of drug.	The frequency of occurrence of heart disorders may increase the	

11. Side effects

The following side effects may occur, so carefully monitor the patient, and if any abnormalities are observed, take appropriate measures such as discontinuing administration. **11.1 Serious side effects**

11.1.1 Cardiac disorders

heart failure (4.5%)

(symptoms: dyspnea, orthopnea, cough, etc.; symptoms/abnormalities: S3 gallop, decreased ejection fraction, peripheral edema, etc.), cardiogenic shock (Pulmonary edema (frequency unknown), pericardial effusion (0.1%), cardiomyopathy (0.4%), pericarditis (frequency unknown), arrhythmia (1.4%), bradycardia (0.1%), etc. were reported. has been done. If abnormalities are observed, consider continuing administration and take appropriate measures only if the therapeutic benefits are judged to outweigh the risks. However, if symptoms are severe, administration should be discontinued and appropriate measures should be taken. [See 1.2, 8.1, 9.1.1-9.1.7]

11.1.2 Infusion reactions (incidence unknown) Infusion reactions (symptoms: fever, chills, nausea, vomiting, pain, headache, cough, nausea) that often occur during administration of this drug or within 24 hours after starting administration.

40% of patients (at the time of approval for metastatic breast cancer with confirmed HER2 overexpression). These symptoms are usually mild to moderate in severity and tend to occur primarily during the first administration of this drug. In addition, among infusion reactions, serious side effects such as shock, anaphylaxis, and lung damage (bronchospasm, severe hypotension, acute respiratory distress syndrome, tachycardia, facial edema, dizziness, tinnitus, dyspnea, asthma, and wheezing) There have been reports of cases in which death occurred due to symptoms such as angioedema, pharyngeal edema, respiratory failure, non-cardiogenic pulmonary edema, pleural effusion, hypoxia, etc.). If any of these abnormalities are observed during administration of this drug, administration should be discontinued immediately. There are no established criteria for determining whether re-administration is appropriate for patients who develop such symptoms. If any abnormality is observed, take appropriate measures (oxygen inhalation, administration of ÿ-agonists/corticosteroids, antipyretic analgesics, antihistamines, etc.) and carefully monitor the patient's condition until the symptoms recover. To do. [See 1.3, 9.1.8, 11.1.3] **11.1.3 Interstitial pneumonia/lung disorder**

Lung disorders such as interstitial pneumonia (0.2%), pulmonary fibrosis (incidence unknown), pneumonia (including allergic pneumonia, etc.) (0.3%), and acute respiratory distress syndrome (less than 0.1%) may occur. [See 1.3, 9.1.8, 11.1.2] **11.1.4** Leukopenia (4.4%), neutropenia (6.9%), thrombocytopenia (1.9%), Anemia (3.7%)

11.1.5 Liver failure (less than 0.1%), jaundice (0.1%), hepatitis (0.1%), liver damage (0.5%) **11.1.6 Renal damage**

Renal failure (0.2%) and renal impairment (1.0%) may occur. **11.1.7** Coma (incidence unknown), cerebrovascular disorder (0.2%), cerebral edema (incidence unknown) **11.1.8** Sepsis (0.2%) **11.1.9 Tumor lysis syndrome**

ÿ **(incidence unknown)** Administer if abnormalities are observed The patient should be discontinued and take appropriate measures (administration of physiological saline, hyperuricemia treatment agents, etc., dialysis, etc.), and the patient's condition should be carefully monitored until the symptoms have resolved. [See 8.3] Note) Expression frequency is based on overseas clinical studies for tumors that overexpress HER2 [H0407g study, H0452g study, H0453g study], overseas clinical studies for metastatic breast cancer that overexpress HER2 [Study H0551g, H0552g study, H0648g study] , H0649g study, H0650g study, H0659g study, H0693g study], Japanese clinical trial for HER2-overexpressing advanced/recurrent breast cancer [MKC-454-02 study], Post-marketing clinical trial for HER2-overexpressing metastatic breast cancer , results survey on the use of HER2-overexpressing breast cancer in metastatic breast cancer, international joint study [HERA study] for breast cancer with HER2 overexpression (adjuvant drug therapy), unresectable progression/recurrence in patients with HER2 overexpression An international collaborative trial for gastric cancer [ToGA trial], a domestic clinical trial for HER2-positive unresectable advanced/recurrent salivary gland cancer [HUON-003-01 trial], and a cure for HER2-positive cancer that has worsened after cancer chemotherapy. Includes a domestic clinical trial [TRIUMPH trial] for unresectable advanced/recurrent colorectal cancer. **11.2 Other side effects 11.2.1 Metastatic breast cancer with confirmed HER2 overexpression**

	10% or more 2	to less than 10% Less	than 2% Frequency unknown Paraesthesia,
mental nervous system		dizziness, ataxia, taste abnormality, anxiety, caries paresis, numbness, numbness, depression, somnolence, -pathy Muscular hypertonia Abnormal dreams Hyperkinesia Epigastric pain, vomiting (16.8%) Constipation, abdominal	Loss of appetite Nausea/vomiting Diarrhea,
digester	pain		
Circulator			Hypotension, tachycardia, vasodilation Flushing, high blood pressure, palpitations,
respirator		fever Dyspnea, cough Pleural effusion, asthma Roughness, nasal bleeding	
blood			prothrombin decrease
skin		loss Erythema, skin dryness, nail disorder, hives, irritation, pruritus Dermatitis, maculoid papular eruption, sweating, acne	
liver			AST increase, Increased ALT
Eye			Increased lacrimation, conjunctivitis, visual
others	impairment Fever (31.5%) Fatigue, upper respiratory tract infection (nasal %), chills Joint pain, pain, inflammation, nasopharyngitis (20.0%), edema, back pharyngitis, secondary Nasal fatigue (10.5 pain, asthenia, cavitis, etc.), chest %) Muscle pain, chest discomfort, bone pain, pain, peripheral floating neck pain, urinary tract, limb pain Infection, hearing loss, infection		

Note) Expression frequency is based on overseas clinical trials for tumors that overexpress HER2 [H0407g trial, H0452g trial, H0453g trial], overseas clinical trials for metastatic breast cancer that overexpress HER2 [H0551g trial, H0552g trial, H0648g trial, H0649g trial, H0650g study, H0659g study, H0693g study], Japanese clinical study for advanced/recurrent breast cancer with HER2 overexpression [Study MKC-454-02], Post-marketing clinical study for metastatic breast cancer with HER2 overexpression and HER2 overexpression This includes a survey of the results of its use in metastatic breast cancer.

11.2.2 Postoperative drug therapy for breast cancer with confirmed HER2 overexpression

	1% or more 0.2	to less than 1% Less	than 0.2% Frequency unknown
mental nervous system	Headache Dizziness, paresthesia, tremor, lethargy, insomnia, taste abnormality, anxiety, depression, vertigo Stomatitis, abdominal pain,		hypoesthesia, neuropathy
digester	nausea, diarrhea, vomiting	epigastric pain, oral Dryness, mouth Indigestion Constipation, gastric ulcer formation, flatulence Hypertension, tachycardia, lymphedema Hot flashes,	
Circulator	palpitations	hypothermia Blood pressure, flushing Difficulty breathing Rhinorrhea, nosebleeds Throat pain Dry nose, pain,	
respirator	cough, ulcers , nasal sinusitis, discomfort bronchitis		
skin	Nail disorders, erythema, acne rash, pruritus		Broken claws, dry skin, cracked skin
kidney		Dysuria,	
others	asthenia, chills, peripheral edema, edema, muscle herpes zoster, breast fever, fatigue, back pain, muscle spasm Skeletal pain, chamber pain, cellulitis, arthralgia, muscle contractions, chest discomfort Cystitis, limb pain, Lacrimation Pain, flu feeling, inflammation of the mucous membranes Urinary tract infections Increase, weight gain Enzyme-like disease, symptoms, fatigue, symptoms, erysipelas, cold sensation, pain Upper respiratory tract infection Bone pain, chest pain, pain, dry mucous membranes, (rhinitis) , nasopharyngeal influenza, blurred vision, musculoskeletal inflammation, pharyngitis, etc.) The Stiffness **11.2.3 Advanced/recurrent gastric cancer that is confirmed**		

to overexpress HER2 and is unresectable 10% or more 2 to less than 10% Taste abnormality, floating Dizziness,

	neuropathy Insomnia, paresthesia Chi Nausea,		Less than
mental nervous system	Loss of appetite,	vomiting, abdominal pain, epigastric pain diarrhea, stomatitis, constipation	2% Headache, lethargy
digester			Indigestion, dry mouth, difficulty swallowing
Circulator		high blood pressure	Palpitations, flushing, orthostatic hypotension

	More than 10	2% to less than 10%	less than 2%
respirator		Hiccups, nosebleeds, coughing, breathing difficulty	
blood		hemoglobin decrease	
skin	Palms and soles redness perception insensitivity full syndrome	pigmentation disorders, alopecia, Nail disorders, rashes, skin drying	pruritus
kidney		renal creatinine chestnut Decreased balance, addictive nephropathy	
others	fatigue, helplessness disease, mucous membranes inflammation, weight reduce	Fever, chills, dehydration, low energy Riumemia, hyponatremia bloodemia, upper respiratory tract infection, hearing loss, Edema, peripheral edema, high blood pressure Reatinemia, oral cavity ÿÿÿ syndrome, tinnitus, allergies	Fatigue, low albumin blood symptoms, weight gain

11.2.4 HER2-positive unresectable advanced/recurrent salivary gland cancer

	30% or more but less than 20-30%		less than 20%
digester			Endostomatitis, upper abdominal pain, vomiting, loss of appetite
respirator		pleural effusion	Bronchitis, difficulty breathing
skin			Onycholysis, dry skin Dryness, alopecia
liver		ALT increase	
			Increased lacrimation
eye blood			Decreased lymphocyte count
others	Fatigue, peripheral Sexual edema, low blood pressure Rubuminaemia		weight gain, facial edema, fever, low calcium bloodemia, blood lactic acid dehydration Increase in enzymes

ÿ **11.2.5 Non-curative resection of HER2-positive patients who progressed after cancer chemotherapy**

Advanced or recurrent colorectal cancer

	20% or more 10-20%	less than 10%	
Digestive system Diarrhea (36.7%) Stomatitis Loss of appetite			
skin			rash
other		Malaise	

14. Application notes

14.1 Precautions when preparing drugs

14.1.1 When preparing this drug, use the following conversion formula per body weight.

Calculate the amount of sample needed for administration.

•Method A:

$$\text{Initial extraction amount (mL)} = \frac{\text{Body weight (kg)} \times 4\ (\text{mg/kg})}{21\ddot{y}\text{mg/mL}\ddot{y}}$$

$$\text{2nd and subsequent times Amount extracted (mL)} = \frac{\text{Body weight (kg)} \times 2\ (\text{mg/kg})}{21\ddot{y}\text{mg/mL}\ddot{y}}$$

•Method B:

$$\text{Initial extraction amount (mL)} = \frac{\text{Body weight (kg)} \times 8\ (\text{mg/kg})}{21\ddot{y}\text{mg/mL}\ddot{y}}$$

$$\text{2nd and subsequent times Amount extracted (mL)} = \frac{\text{Body weight (kg)} \times 6\ (\text{mg/kg})}{21\ddot{y}\text{mg/mL}\ddot{y}}$$

14.1.2 When preparing, use other than JP Water for Injection and JP Physiological Saline

Do not use.

ÿÿ **14.1.3** Protein aggregation occurs when mixed with glucose solution

Therefore, JP water for injection (60 for injection: 3.0mL, 150 for injection:

Trastuzumab (genetical recombination) dissolved in 7.2mL)

After adjusting the concentration to 21 mg/mL, draw out the required amount with a syringe,

Immediately dilute to 250 mL of JP physiological saline.

14.1.4 This product contains polysorbate and foams easily.

Therefore, when dissolving, gently mix by inverting until the bubbles almost disappear.

Leave it for a few minutes.

14.1.5 Prepare at the time of use and use immediately after preparation. Also,

Discard remaining liquid.

14.2 Precautions when administering drugs

14.2.1 When this drug is mixed with 5% glucose solution, protein aggregation may occur.

Avoid mixing with glucose solutions, and avoid mixing this drug with glucose solutions.

Do not co-administer sucrose solution using the same IV line.

thing.

14.2.2 Do not co-inject with other drugs.

15. Other notes

15.1 Information based on clinical use

15.1.1 Anti-trastuzumab antibodies appeared after administration of this drug.

There is a report (1 case out of 921 cases), but there were no side effects in this case.

I was not able to admit.

15.1.2 Acute leukemia may occur in patients taking this drug concomitantly with other antineoplastic agents.

There have been reports of blood disease and myelodysplastic syndrome (MDS) occurring.

be.

15.1.3 Randomized controlled trials have shown that other anti-inflammatory drugs with myelosuppression

When this drug is used in combination with an anti-cancer agent, the anti-cancer agent alone

It was reported that the incidence of febrile neutropenia was increased compared to

There is.

16. Pharmacokinetics

16.1 Blood concentration

16.1.1 Single dose

Trastuzumab in 18 Japanese patients with HER2-overexpressing breast cancer

The serum concentration when 8mg/kg Note 1) was intravenously infused for 90 minutes is as follows:

Met. Trastuzumab disappears slowly from serum, and

The half-life calculated by applying the 1-compartment model for each patient is

The period increased as the dose increased; at a dose of 1 mg/kg Note 1), the period increased for 2.4 days, and at a dose of 8 mg/kg.

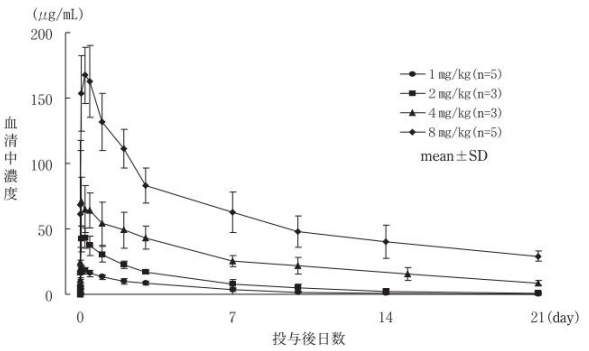
kg was 5.5 days. The maximum serum concentration (Cmax) increases dose-proportionally.

Clearance (CL) decreased as the dose increased.

did. Volume of distribution (Vd) did not change with increasing dose;

It was approximately equivalent to the plasma volume 6).

Serum trastuzumab concentration over time after single administration



Pharmacokinetic parameters of trastuzumab after single administration

Dose (mg/kg)	Number of cases	Cmax (ÿg/mL)	AUCinf ÿÿg•day/mLÿ	t1/2 ÿdayÿ	CL ÿmL/day/kgÿ	CEO (mL/kg)
1	5	ÿÿ 19±2.8	ÿÿ 66±15	2.4±0.4	16±3.8	55±7.5
2	3	ÿÿ 43±8.5	154±16	2.6±0.7	13±1.4	49±12
4	3	544±68	875±91	7.4±1.0	63±15	
8	5	177±19	1,261±330	5.5±1.5	6.8±2.4	51±6.5

mean±SD

Note 1) Approved dosage and administration is 4mg/kg for the first dose, and from the second dose onward.

2 mg/kg once a week (method A) and 8 mg/kg for the first dose, second dose

Thereafter, 6 mg/kg was administered once every 3 weeks (Method B).

16.1.2 Repeated administration

(1) Trastuzumab in 18 Japanese patients with HER2-overexpressing breast cancer

From day 21 after 8 mg/kg Note 1) is infused for 90 minutes, intravenous infusion is administered once a week for 90 minutes.

When repeated administration, the minimum (Cmin) and maximum on day 43 after the first administration

The high serum concentrations (Cmax) were as follows7).

Minimum and maximum serum trastuzumab concentrations after repeated administration

Dose ymg/kgÿ 1	Number of cases	Cmin (ÿg/mL)	Cmax (ÿg/mL)
	4	6.72±0.869 2.14ÿ	26.7±3.18
	2	24.7 74.9ÿ116	60.1ÿ64.4
2 4	2	200±20.6	134ÿ220
8	4		327±41.6

1ÿ8mg/kgÿmean±SD

(2) Patients including Japanese patients in postoperative drug therapy for HER2-overexpressing breast cancer

Trastuzumab was administered to 8 patients at 8 mg/kg for the first dose and 6 mg/kg for the second and subsequent doses.

kg was administered by intravenous infusion over 90 minutes once every 3 weeks. steady state reached

Drugs calculated by model-independent analysis in cycle 18

The physical kinetic parameters were as follows8).

Pharmacokinetic parameters of trastuzumab upon repeated administration

Case Number of cases		Cmin (ÿg/mL)	Cmax (ÿg/mL)	AUC0-21d ÿÿg•day/mLÿ	CLss ÿL/dayÿ	t1/2 Note 2) ÿdayÿ
Japanese 3	58.5±21.6	203±19	Foreigner	2067±551	0.171±0.058	16.7±5.3
5	71.2±23.2	215±5		2289±297	0.188±0.027	16.3±3.8

mean±SD

Note 2) Half-life of final phase

(3) Initial use of trastuzumab in 213 patients with HER2-overexpressing breast cancer

When repeated intravenous infusions of 4 mg/kg and 2 mg/kg from the second dose onward once a week, shed

High baseline concentration of antigen (HER2 extracellular region released from tumor)

The minimum serum concentration (Cmin) of trastuzumab in cases with a low value

9) (foreigner data).

16.1.3 Population pharmacokinetic analysis

476 patients with HER2-overexpressing breast cancer (3 patients had non-breast cancer)

Lastuzumab: 4 mg/kg for the first time, 2 mg/kg for subsequent doses once a week for 90 minutes

Serum after repeated intravenous infusion (16 patients received a single dose of 10 to 500 mg)

Population pharmacokinetics analysis was performed using intermediate concentrations. Mo

As a result of deliberation, a 2-compartment model was selected, and the half-life (t1/2)

was 28.5 days (population mean, 95% confidence interval: 25.5 to 32.8 days)10)

(Foreign data).

Trastuzumab drug obtained from population pharmacokinetics analysis

Physical kinetic parameters

CminNote 3) (ÿg/mL)	Cmax note 3) (ÿg/mL)	AUC note 3) ÿmg•day/Lÿ	t1/2 ÿdayÿ	CL ÿL/dayÿ
66	110	578	28.5	0.225

Note 3) Predicted value at steady state (reached in about 20 weeks) when administered using Method A

16.3 Distribution

Nude mice with HER2-overexpressing tumors subcutaneously implanted with 125I-labeled

When a single intravenous dose of lastuzumab (10 mg/kg) was administered, radioactivity

The migration into normal tissues was low. Radioactivity in tumor 24 hours after administration

After reaching the highest level, it remained higher than in normal tissue, and the serum concentration

It gradually decreased at almost the same concentration 11). Most of the radioactivity in serum is from truss.

It was tuzumab12).

16.5 Excretion

16.5.1 HER2 overexpressing breast cancer patients

Trastuzumab in 18 Japanese patients with HER2-overexpressing breast cancer

When 8 mg/kg Note 1) was injected intravenously for 90 minutes, the unchanged drug was injected 24 hours after administration.

The urinary excretion rate was less than 0.01%13).

16.5.2 Normal mouse

125I-labeled trastuzumab (10 mg/kg) was administered to normal mice (ICR strain).

When administered intravenously, radioactivity is excreted in the urine and feces for up to 7 days after administration.

Excretion rates are 31% and 2% for males, respectively, and 28% and 5% for females, respectively.

Met. Up to 76 days after administration, the rates were 83% and 12% in males, respectively;

In females, the rates were 65% and 29%, respectively14). However, trastuz in the urine

Mab was rarely observed12).

17. Clinical results

17.1 Efficacy and safety studies

<Breast cancer with confirmed HER2 overexpression>

17.1.1 Domestic phase I clinical trial (Study MKC-454-02)

This drug was administered to patients with metastatic breast cancer overexpressing HER2 (1-

8mg/kg) Note 1). The results of antitumor effects are shown in the table below15).

Side effects occurred in 14/18 cases (77.8%). The main side effects were fever (44.4%);

AST increased in 22.2%, vomiting in 16.7%, chills in 16.7%, and fatigue in 16.7%.

Antitumor effect on HER2 overexpressing breast cancer patients

Dose	CR	PR	MR	NC	PD	NE	Total					
1mg/kg	4	6						1		1		
2mg/kg	2	3				1						
4mg/kg	2	3		1								
8mg/kg						2	1	1	1	6		
	1	2ÿ11.1ÿ				3	2	9	2	18		

NE: Not Evaluate The

Number of cases (%)

administration period of this drug in the above 18 cases was 1 to 10 weeks (median: 10 weeks).

It was. Additionally, the drug was not administered to elderly people (65 years or older). Note 1)

Approved dosage and administration is 4mg/kg for the first dose, and from the second dose onward.

2 mg/kg administered at 1-week intervals (method A) and 8 mg/kg at first dose;

From the second dose onwards, 6mg/kg was administered at 3-week intervals (Method B).

17.1.2 Overseas phase II clinical trial (H0551g study)

This drug was administered alone to patients with metastatic breast cancer that overexpressed HER2 (first time).

Administer 250mg once, then 100mg every 7 days for 10 weeks) Note 1). Evaluation possible

Of the 43 patients who responded, 5 (11.6%) responded.16)

Side effects occurred in 28/46 cases (60.9%). The main side effects are cold

21.7%, fever 17.4%, diarrhea 15.2%, etc.

17.1.3 Overseas phase II clinical trial (H0552g study)

This drug is being used in combination with cisplatin for patients with metastatic breast cancer that overexpresses HER2.

Administered in combination (initial dose 250 mg, subsequent doses 100 mg every 7 days for 8 weeks)

(Note 1). Of the 37 evaluable cases, 9 responded (24.3%)17).

Side effects occurred in 22/39 cases (56.4%). The main side effect is asthenia

28.2%, fever 18.0%, nausea 18.0%, chills 15.4%, leukopenia

It was 15.4% etc.

17.1.4 Overseas phase III clinical trial (H0648g study)

This drug can be used in conjunction with other chemotherapy in patients with metastatic breast cancer that overexpresses HER2.

Administered in combination (4 mg/kg for the first time, 2 mg/kg for the second and subsequent doses at 1-week intervals)

(administered). The primary endpoint, the median time to disease progression,

9.08 patients in the ntracycline + cyclophosphamide (AC) combination group.

6.48 months for AC alone group, 6.87 months for paclitaxel combination group,

The survival time for the clitaxel alone group was 2.89 months. By degree of HER2 overexpression

The median time to disease progression in the AC combination group was 9.05 months in the 3+ group.

month, 9.11 months in the 2+ group and 7.14 months in the 3+ group in the paclitaxel combination group.

month, and the 2+ group was 5.30 months. There were 80/143 responders in the AC combination group.

(55.9%), and 38/92 patients (41.3%) in the paclitaxel combination group18).

Side effects occurred in 122/143 patients (85.3%) in the AC combination group and in the paclitaxel combination group.

In the group, it occurred in 78/91 cases (85.7%). The main side effects were in the AC combination group.

28.7% had fever, 25.9% nausea, 25.2% asthenia, 23.8% chills, and vomiting.

18.9%, diarrhea 18.2%, pain 17.5%, dyspnea 16.1%, etc., ÿÿÿÿÿ

In the cell combination group, 36.3% experienced chills, 35.2% asthenia, 29.7% fever, and nausea.

23.1%, pain 22.0%, diarrhea 19.8%, rash 17.6%, vomiting 17.6%, etc.

17.1.5 Overseas phase III clinical trial (H0649g study)

HER2 overexpression with recurrence after 1-2 prior chemotherapy regimens

This drug was administered to patients with metastatic breast cancer (initial dose of 4 mg/kg, 2

After the first dose, 2 mg/kg was administered at 1-week intervals). The primary endpoint, anti-

Regarding tumor efficacy, there were 34 responders out of 222 patients in the ITT analysis population.

Of the 207 evaluable cases, 34 responded (16.4%).

Median time to disease progression was 3.1 months. HER2 overexpression

The median time to disease progression by grade was 3.3 months for the 3+ group and 3.3 months for the 2+ group.

The age in the group was 1.9 months 19).

Side effects occurred in 182/213 patients (85.4%). The main side effect is fever

36.6%, chills 35.2%, asthenia 27.2%, nausea 21.1%, pain 17.8%,

The incidence of headache was 15.0%.

17.1.6 Overseas clinical study (H0650g study)

This drug is intended for patients with metastatic breast cancer that overexpresses HER2 and has not been treated with chemotherapy.

(4 mg/kg or 8 mg/kg for the first time, 2 mg/kg for each subsequent time)

kg or 4 mg/kg at weekly intervals Note 1)). Antitumor, the primary endpoint

Regarding efficacy, the response rate of evaluable cases was 7/33 in the 4 mg/kg ÿ 2 mg/kg group.

(21.2%), and 8/29 patients (27.6%) in the 8 mg/kg ÿ 4 mg/kg group20).

Side effects occurred in 40/59 cases (67.8%) in the 4mg/kg ÿ 2mg/kg group, and in the 8mg/kg group.

In the kgÿ4mg/kg group, it occurred in 47/55 cases (85.5%). Main side effects

In the 4 mg/kg ÿ 2 mg/kg group, asthenia 20.3%, pain 20.3%, and coldness occurred.

20.3%, fever 18.6%, etc. In the 8 mg/kg ÿ 4 mg/kg group, 29.1% had fever,

25.5% had fever, 25.5% had asthenia, 18.2% had nausea, and 16.4% had pain.

17.1.7 Overseas clinical study (H0659g study) [continuation study from H0648g study]

Participated in an overseas phase III clinical trial (H0648g trial) and showed progress in metastatic breast cancer.

This drug was administered to confirmed patients (radiotherapy, chemotherapy,

Can be used in combination with immunotherapy and hormonal therapy). 155 evaluable cases

There were 22 patients (14.2%) who responded 21).

The main side effects were asthenia (18.4%), chills (18.4%), fever (16.4%), and nausea.

It was 15.6% etc.

17.1.8 Overseas clinical study (H0693g study)

HER2 excess with recurrence after 3 or more chemotherapy regimens

This drug is used in combination with standard cancer chemotherapy for patients with metastatic breast cancer.

(4 mg/kg for the first time, 2 mg/kg for the second and subsequent doses at one-week intervals)

given). Among the evaluable cases, the response rate was 5/154 (3.2%)22). Side production

Symptoms occurred in 240/360 cases (66.7%). The main side effects were fever (26.7%);

25.8% had chills, 10.6% had asthenia, and 10.3% had nausea.

17.1.9 Global phase III study (HERA study)

In patients with operable breast cancer that overexpresses HER2, surgery, systemic preoperative or postoperative

For patients who have completed post-drug therapy and radiation therapy (if indicated)

Elephant Note 2), this drug was administered at 8 mg/kg (body weight) for the first time and 6 mg/kg for 3 weeks thereafter.

A group administered for 1 year or 2 years at intervals, and a group not administered this drug.

The effectiveness was compared with the control group. In addition, in the group receiving this drug, periodic

Based on the LVEF evaluation, it was decided whether to continue or discontinue administration of this drug.

Interim analysis results: An interim analysis was conducted after a median observation period of 12 months, and the incidence of events related to disease-free survival Note 3) was significantly improved in the 1-year treatment group compared to the control group. In addition, the event incidence rate in the same time point analysis of subjects enrolled in Japan in this study was 7.3% (3/41) in the 1-year treatment group and 13.0% (6/46) in the control group23).

In the HERA study, of the 1,678 patients who received this drug, 600 (35.8%) had side effects. Main side effects were chills in 75 cases (4.5%), headache in 61 cases (3.6%), fever in 58 cases (3.5%), nausea in 52 cases (3.1%), fatigue in 51 cases (3.0%), and decreased ejection fraction. There were 51 cases (3.0%). Among the 41 domestic cases that participated in this study, side effects were observed in 23 cases (56.1%), with the main side effects being chills in 6 cases (14.6%), fever in 5 cases (12.2%), and fatigue in 5 cases (12.2%). %), headache in 5 cases (12.2%), and nail disorders in 5 cases (12.2%).

Final analysis results: The final analysis was performed after a median observation period of 8 years. The event rate related to disease-free survival was significantly improved in the 1-year administration group compared to the control group. Comparisons between the 2-year treatment group and the 1-year treatment group were conducted on subjects who were disease-free and alive 12 months after randomization. The event rate regarding disease-free survival in the 2-year treatment group was 23.6% (367/1,553), and no significant improvement was observed compared to the 1-year treatment group (23.6% [367/1,552]) (HR: 0.99, P=0.86)24). Regarding safety, 3,355 patients (1,682 patients in the 1-year treatment group and 1,673 patients in the 2-year treatment group) were included in the analysis, including grade 3 or 4 adverse events and asymptomatic or mildly symptomatic left ventricular ejection. There was a tendency for the incidence of decreased LVEF to be higher in the 2-year treatment group than in the 1-year treatment group [Grade 3 or 4 adverse events: 16.3% (275/1,682 patients) in the 1-year treatment group; 20.4% (342/1,673 patients) in the 2-year treatment group, asymptomatic or mildly symptomatic decreased left ventricular ejection fraction: 4.1% (69/1,682 patients) in the 1-year treatment group, 7.2% (120 patients) in the 2-year treatment group. /1,673 cases)] [See 7.2.2] Note 2) The HERA study targeted patients with primary breast cancer that was non-metastatic and could be treated with radical surgery. Patients with negative axillary lymph node metastases, tumors less than 1 cm in diameter, and patients who were not eligible for chemotherapy were excluded. Note 3) Recurrence of breast cancer (regardless of location), contralateral breast cancer, development of secondary cancer other than breast cancer (excluding basal cell carcinoma and squamous cell carcinoma of the skin, and carcinoma in situ of the cervix), death (cause of death) Comparison of event rates related to disease-free survival between 1-year treatment group and control group

		Number of cases	Event Note 3) Occurrence Number of cases (incidence rate)	Hazard ratio P value	
Observation period Median At 12 months	Control group	1693	219ÿ12.9%ÿ	0.54	ÿ0.0001
	1 year treatment	group 1693	127ÿ 7.5%ÿ		
Median observation period At 8 years	Control group Note 4)	1697 Note 5)	570 (33.6%)	0.76	ÿ0.0001
	1-year treatment	group 1702 Note 5)	471 (27.7%)		

Note 4) For the control group, administration of this drug was started after the interim analysis results were announced. 52.1% (884/1,697) of cases were included. Note 5) Cutoff for analysis at median observation period of 12 months Because the trial included a small number of subjects randomized later than Therefore, there is a difference in the number of cases.

<Unresectable advanced/recurrent gastric cancer with confirmed HER2 overexpression>

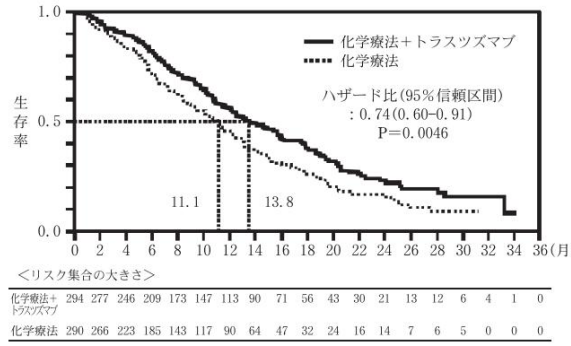
17.1.10 International joint phase III study (ToGA study)

Progressive/recurrent gastric cancer with HER2 overexpression (IHC method 3+ or FISH method positive) conducted chemotherapy in 584 patients with adenocarcinoma of the gastroesophageal junction (untreated with chemotherapy). therapy (capecitabine + cisplatin or fluorouracil + cisplatin)

A phase III clinical trial was conducted to compare chemotherapy (platin) and chemotherapy + this drug. Ta. This drug is administered at 8 mg/kg (body weight) for the first time, and at 6 mg/kg for subsequent doses at 3-week intervals, at the same dosage and administration until disease progression is observed after chemotherapy is discontinued. Administration was continued. Chemotherapy consisted of capecitabine 1000 mg/m2 administered orally twice a day for 14 days or fluorouracil 800 mg/m2 administered intravenously for 5 days Note 6) and cisplatin 80 mg/m2 administered intravenously at 3-week intervals. At the interim analysis at 75% of the target number of events, chemotherapy plus Compared to chemotherapy alone, this drug has significantly improved overall survival, the primary endpoint. A significant prolongation was observed. Of the 584 cases, the details of chemotherapy were as follows: Capecitabine + cisplatin in 511 cases, fluorouracil + cisplatin in 511 cases; There were 73 cases of latin. In Japan, capecitabine + cisplatin was used in all cases (101 cases)25).

Of the 294 patients who received this drug in the ToGA study, 283 cases had side effects. (96.3%). The main side effects were nausea in 186 cases (63.3%); 157 cases (53.4%) had neutropenia, 129 cases (43.9%) had vomiting, and 121 cases had loss of appetite. (41.2%), fatigue in 87 cases (29.6%), diarrhea in 85 cases (28.9%), onset of palms and soles. There were 72 cases (24.5%) of red sensation syndrome and 66 cases (22.4%) of stomatitis. Ta. Of these, 51 domestic cases that participated in this study showed no side effects. was observed in 50 patients (98.0%), and the main side effects were anorexia in 43 patients (84.3%), nausea in 41 patients (80.4%), renal dysfunction in 31 patients (60.8%), and neutropenia in 30 patients (58.8%), vomiting in 29 cases (56.9%), fatigue in 29 cases (56.9%), stomatitis in 26 cases (51.0%), hiccups in 20 cases (39.2%), palmar/plantar erythrodysesthesia syndrome in 19 cases (37.3 %) and constipation in 18 cases (35.3%). [See 5.4, 7.3] Note 6) Domestic approved usage and dosage of fluorouracil in combination with other antineoplastic agents: As fluorouracil, the usual adult dose of 5 to 10 mg/kg per day is used in combination with other antineoplastic agents. Follow the instructions for single use, or use intermittently once or twice a week. When used alone: As fluorouracil, the usual adult dose is 5 to 15 mg/kg per day, once daily for the first 5 days, by intravenous injection or intravenous drip. Thereafter, administer 5 to 7.5 mg/kg intravenously or as an intravenous drip once a day every other day. The dosage may be increased or decreased as appropriate depending on age and symptoms.

Kaplan-Meier curve for overall survival



<HER2-positive advanced/recurrent salivary gland cancer that cannot be completely resected>

17.1.11 Domestic phase II study (HUON-003-01 study) Complete cure for HER2 positive (IHC method 3+ or IHC method 2+ and DISH method positive Note 7)

This drug was administered to 16 patients with advanced or recurrent unresectable salivary gland cancer. Administered in combination with taxel. This drug is administered at an initial dose of 8 mg/kg (body weight), subsequent doses are 6 mg/kg, and docetaxel is administered at 70 mg/m2 at 3-week intervals, for a maximum of 8 cycles unless disease progression or study discontinuation criteria are met. Continued. The primary endpoint, the centrally judged response rate [95% confidence interval] based on RECIST ver. 1.1, was 60.0% [32.3, 83.7]26). Side effects occurred in 12/16 cases (75.0%). The main side effects are neutrophil count 10 cases (62.5%) were reduced, 9 cases (56.3%) were anemic, 9 cases (56.3%) were reduced in white blood cell count, Malaise in 6 cases (37.5%), peripheral edema in 6 cases (37.5%), hypoalbuminemia 5 cases (31.3%), infusion-related reactions in 4 cases (25.0%), ALT increase in 4 cases (25.0%), There were 4 cases of pleural effusion (25.0%).

Note 7) All 16 registered cases were IHC 3+.

ÿUnresectable progression/recurrence of HER2-positive disease that worsened after cancer chemotherapy colorectal cancer>

17.1.12 Domestic phase II study (TRIUMPH study) *

This drug was administered in combination with pertuzumab to 30 patients with HER2-positive, unresectable, advanced or recurrent colorectal cancer (Note 9) who had a history of chemotherapy . This drug was administered at 8 mg/kg (body weight) for the first time and 6 mg/kg for the second and subsequent doses, and pertuzumab was administered at 840 mg for the first time and 420 mg for the second and subsequent doses at 3-week intervals, and continued until disease progression or study discontinuation criteria were met. In the main endpoint Response rate [95%] determined by the investigator based on RECISTver.1.1 Confidence interval] is HER2-positive patient population tested using tumor tissue. 29.6% [13.8,50.2] (8/27 cases), and 28.0% [12.1,49.4] (7/25 cases) in the patient population with HER2-positive blood samples. Side effects occurred in 24/30 cases (80.0%). The main side effects are reactions associated with injection. 14 cases (46.7%), diarrhea in 11 cases (36.7%), stomatitis in 4 cases (13.3%), fatigue in 3 cases (10.0%), etc.27). [See 5.10]

Note 8) Fluorinated pyrimidine anti-cancer agents, oxaliplatin, Notecan hydrochloride hydrate and anti-epidermal growth factor receptor (EGFR) Refractory or non-responsive to antibody drugs (cetuximab or panitumumab) Patients who tolerated the study were enrolled.

Note 9) In tumor tissue specimens RAS Confirmed that the gene is wild type. and the following has been determined by testing using tumor tissue or blood specimens: Patients who met any of the following were eligible. In addition, tumor tissue All 27 patients enrolled based on test results using FISH 23 cases and 4 cases were positive for IHC method 3+ and 2+, respectively. It was an example. Test using tumor tissue: IHC method 3+ or FISH method for HER2 Positive Test using blood samples: HER2 gene detection using next-generation sequencing Gene amplification (gene copy number 2.4 or more) and RAS gene wild

type (in cell-free DNA, the ratio of genetic mutations to the most frequently detected genetic mutations is 30% or less) RAS

18. Pharmacology

18.1 Mechanism of action

After specifically binding to HER2, this drug exerts antitumor effects through antibody-dependent cytotoxicity (ADCC) using NK cells and monocytes as active cells28),29) . Another possible mechanism is that by reducing the number of HER2 molecules, cell proliferation signals are reduced, and as a result, this drug directly suppresses cell proliferation30).

18.2 Antitumor effect

Nude mouse transplantable human breast cancer with high HER2 expression (MCF7-HER2, Antitumor effects were observed against BT-474 (number of HER2 receptors per cell = 1.0 x 106)) and human gastric cancer (NCI-N87)31)-33). Also, In NCI-N87, an enhanced antitumor effect was observed when used in combination with other antineoplastic agents34).

For MCF-7-HER2, the total dose ranges from 3 to 100 mg/kg (3 doses); for NCI-N87, the total dose ranges from 70 to 280 mg/kg (6 doses). It showed a dose-dependent growth-inhibiting effect 31), 33). On the other hand, BT-474 showed a dose-dependent growth-inhibiting effect in the daily dose range of 0.1 to 30 mg/kg (8 to 10 doses), and in the high-dose group of 1 mg/kg or more, it showed tumor-inhibiting effects. Complete regression of the tumor was also observed32). **18.3 Antibody-dependent cytotoxicity (ADCC)**

Human peripheral blood mononuclear cells treated with human Interleukin-2 were used as working cells. Mix the following target cells pre-labeled with Na51CrO4 at a ratio of active cells: target cells = 25:1, 12.5:1, 6.25:1, 3.13:1, add 0.1 ÿg/mL trastuzumab, and culture for 4 hours. (37ÿ, 5%CO2). ADCC activity was measured by chrome release assay.

Human mammary gland epithelial cell line 184A1 (HER2 expression level Note) = 0.3) Human breast cancer cell line MCF7 (HER2 expression level = 1.2) Human gastric cancer cell line MKN7 (HER2 expression level = 16.7) Human breast cancer cell line SK-BR-3 (HER2 expression level = 16.7) Expression level = 33.0)

Note) Relative value when the HER2 expression level of 184 human mammary epithelial cell lines is set to 1.0. As a result, there is a high correlation between cytotoxic activity and HER2 expression level at any active cell: target cell ratio. (R2 = 0.93, 0.92, 0.87, 0.66 when effector cell: target cell = 25:1, 12.5:1, 6.25:1, 3.13:1, respectively), and trastuzumab inhibited HER2-high expressing cells. It was shown to exert stronger cytotoxic activity29). However , in a tumor line with low HER2 expression (MCF7), trastuzumab-induced ADCC activity was extremely weak in a test, and direct cell growth inhibition (trastuzumab's mouse parent antibody 4D5) 28) in vitro

18.4 Inhibition effect on the number of HER2 molecules

Human breast cancer cell SK-BR-3 (HER2 high level expression line (per cell) HER2 receptor number = 9.0 × 105)) and MCF7 (HER2 low-level expressing strain (HER2 receptor number per cell = 2.2 × 104)) were cultured for 1 or 5 days in the presence or absence of 150 ÿg/mL of this drug. After that, we determined the number of HER2 cells in the cells, and found that the HER2 levels decreased in all cells30).

19. Physical and chemical findings regarding active

ingredients Generic name: Trastuzumab (genetical recombination)

(Trastuzumab (Genetical Recombination)) (JAN) Molecular formula: Light chain (C1032H1603N277O335S6) Heavy chain (C2192H3387N583O671S16)

Molecular weight: 148,000

Structural formula: 2 molecules of light chain with 214 amino acids and 2 molecules of heavy chain with 449 amino acids glycoprotein

21. Approval conditions

Develop a drug risk management plan and implement it appropriately.

ÿÿ **22. Packaging**

ÿHerceptin Injection 60ÿ

1 vial **<150 for**

Herceptin injection>

1 vial

ÿ **23. Main documents**

1) Public notification by the Committee on Unapproved and Off-label Drugs with High Medical Needs Report on applicability to request: Trastuzumab (genetical recombination) Neoadjuvant chemotherapy for breast cancer with confirmed HER2 overexpression

2) Public notification by the Committee on Unapproved and Off-label Drugs with High Medical Needs Report on applicability to request: Trastuzumab (genetical recombination) Postoperative adjuvant chemotherapy for breast cancer confirmed to overexpress HER2 Addition of dosage and administration for method A (administered at 1-week intervals)

3) Public notification of unapproved drugs and off-label drugs with high medical necessity Report on applicability to request: Trastuzumab (genetical recombination) For metastatic breast cancer with confirmed HER2 overexpression, once administered for 3 weeks. Addition of usage and dosage

4) Animal experiments Fetal transferability (Approved on April 4, 2001, go to application materials summary.2-2-3ÿ

5) Animal experiment: Transfer into milk (Approved on April 4, 2001, go to application document summary.2-4-2ÿ

6) Domestic phase I study - blood concentration at first administration (approved on April 4, 2001, Go to application materials summary.3-1-1-2)

7) Domestic phase I study - Blood concentration after repeated administration (approved on April 4, 2001, Go to application materials summary.3-1-2-4)

8) Internal material: Pharmacokinetics (PK substudy in the HERA study) Interim analysis resultsÿ

9) Overseas phase III study - Repeated administration (approved on April 4, 2001, summary of application materials) 3-1-2-3)

10ÿBruno R, et al. Cancer Chemother Pharmacol. 2005;56:361-9.

11) Animal experiments Concentrations in organs and tissues (approved on April 4, 2001, summary of application materials) To the point.2-2-1)

12) Animal experiments Metabolites (Approved on April 4, 2001, see application document summary.2-3-1)

13) Domestic phase I study - Excretion (Approved on April 4, 2001, go to application data summary.3-2-1ÿ

14) Animal experiments Urinary and fecal excretion (Approved on April 4, 2001, go to application document summary.2-4-1ÿ

15) Domestic Phase I clinical trial (Study MKC-454-02) (Approved on April 4, 2001, Application materials summary T.1-1-1-1)

16) Overseas phase II clinical trial (H0551g study) (Approved and filed on April 4, 2001) Material summary T.2-3-1)

17) Overseas phase II clinical trial (H0552g study) (Approved and filed on April 4, 2001) Material summary T.2-3-2)

18) Overseas phase III study (H0648g study) (Approved on April 4, 2001, application materials Overview T.2-4-1)

19) Overseas phase III study (H0649g study) (Approved on April 4, 2001, application materials Overview T.2-4-2)

20) Overseas clinical study (H0650g study) (Approved on April 4, 2001, Application document summary T.2-5-1)

21) Overseas clinical study (Study H0659g) (Approved on April 4, 2001, Application Materials Summary T.2-5-2)

22) Overseas clinical study (Study H0693g) (Approved on April 4, 2001, Application document summary T.2-5-3)

23) Internal data: Clinical results (HERA study - interim analysis results)

24) Goldhirsch A, et al. Lancet. 2013;382:1021-8. 25) Internal material: Clinical results (ToGA study)

26) Internal document: Domestic phase II study <HUON-003-01 study>

27) Internal data: Clinical results (TRIUMPH study)

28ÿLewis GD, et al. Cancer Immunol Immunother. 1993;37:255-63.

29) Mechanism of action <Antibody-dependent cellular cytotoxicity (ADCC)> (April 4, 2001 Approval, application materials summary E.1-1-1)

30) Mechanism of action (HER2 receptor number suppression effect) (Approved and filed on April 4, 2001) Material summary E.1-1-5)

31ÿPietras RJ, et al. Oncogene. 1998;17:2235-49.

32) Baselga J, et al. Cancer Res. 1998;58:2825-31.

33) Fujimoto-Ouchi K, et al. Cancer Chemother Pharmacol. 2007;59:795-805. 34) Internal material: Antitumor effect

<Antitumor effect in human gastric cancer xenograft model Examination of tumor effect>

24. References request and inquiries

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Tel: 0120-189706
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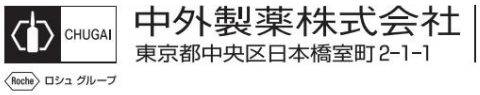
https://www.chugai-pharm.co.jp/

26. Manufacturers, etc.

26.1 Manufacturer



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