Anti-malignant Tumor Agent with Anti-HER2 Humanized Monoclonal Antibody:
Biologics, Designated drug, Prescription drug

薬価基準収載

ハーセプチン®

HERCEPTIN Injection 60
HERCEPTIN Injection 150

Herceptin®

Trastuzumab (genetical recombination) preparation

*1) HER2: Human Epidermal Growth Factor Receptor Type 2
Also referred to as *c-erb*B-2
*2) Use only pursuant to the prescription from a physician, etc

Chugai Pharmaceutical Co., Ltd.
Oncology Area, Scientific Group 2, Breast Cancer Group
Takehiro Yamaguchi, Herceptin Product Manager

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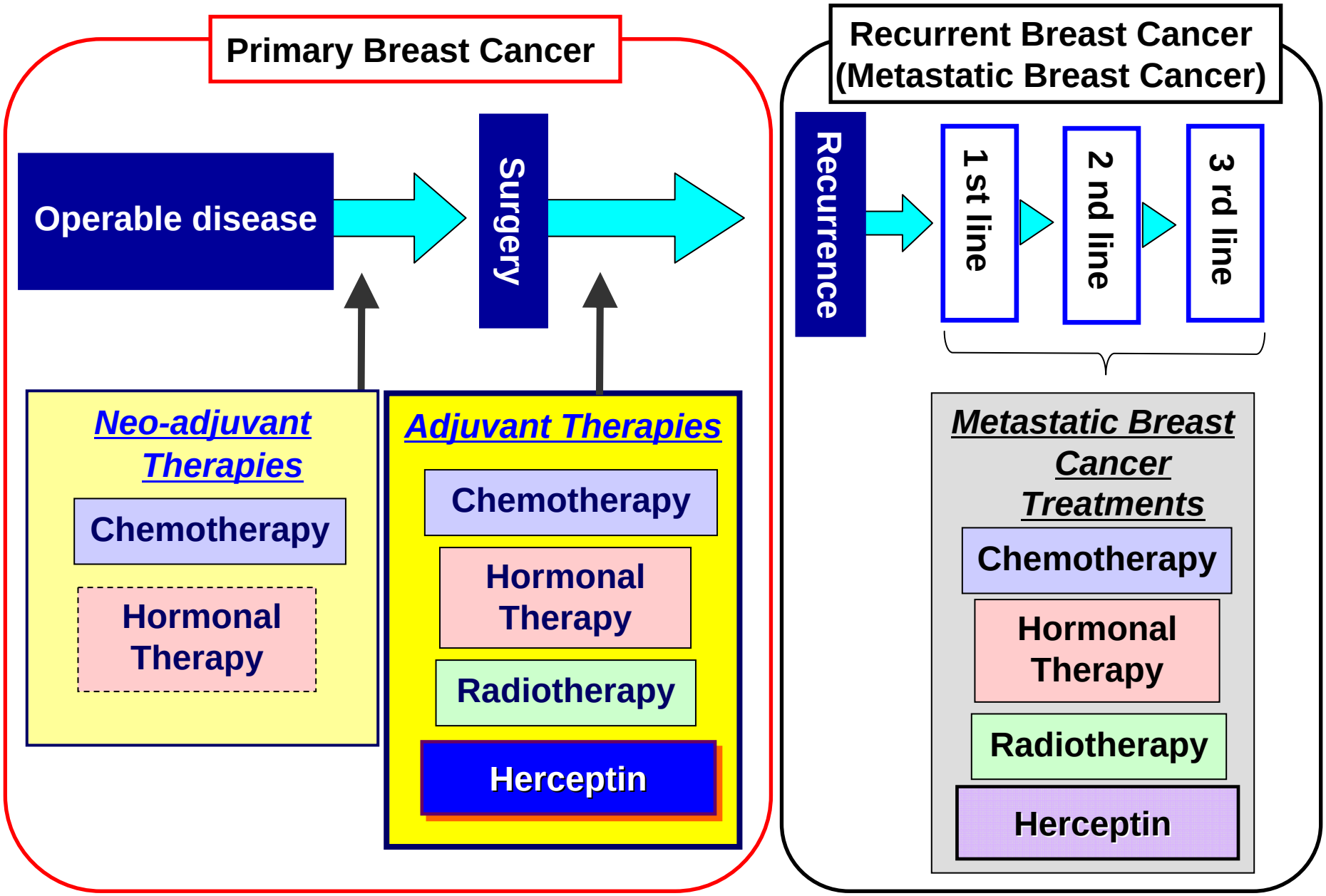
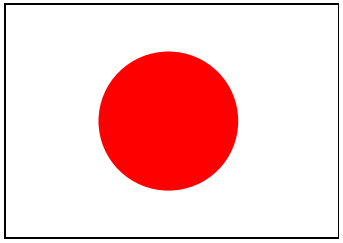
Breast Cancer Treatment Algorithm and Clinical Positioning of Herceptin



Global Situation

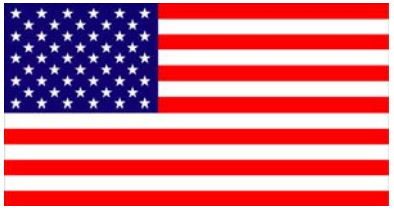
Japan

- Launched in June 2001
- Extension of Indication as Adjuvant Therapy in February 2008



US

- Launched in October 1998
- Extension of Indication as Adjuvant Therapy in November 2006



EU

- Launched in August 2000
- Extension of Indication as Adjuvant Therapy in May 2006

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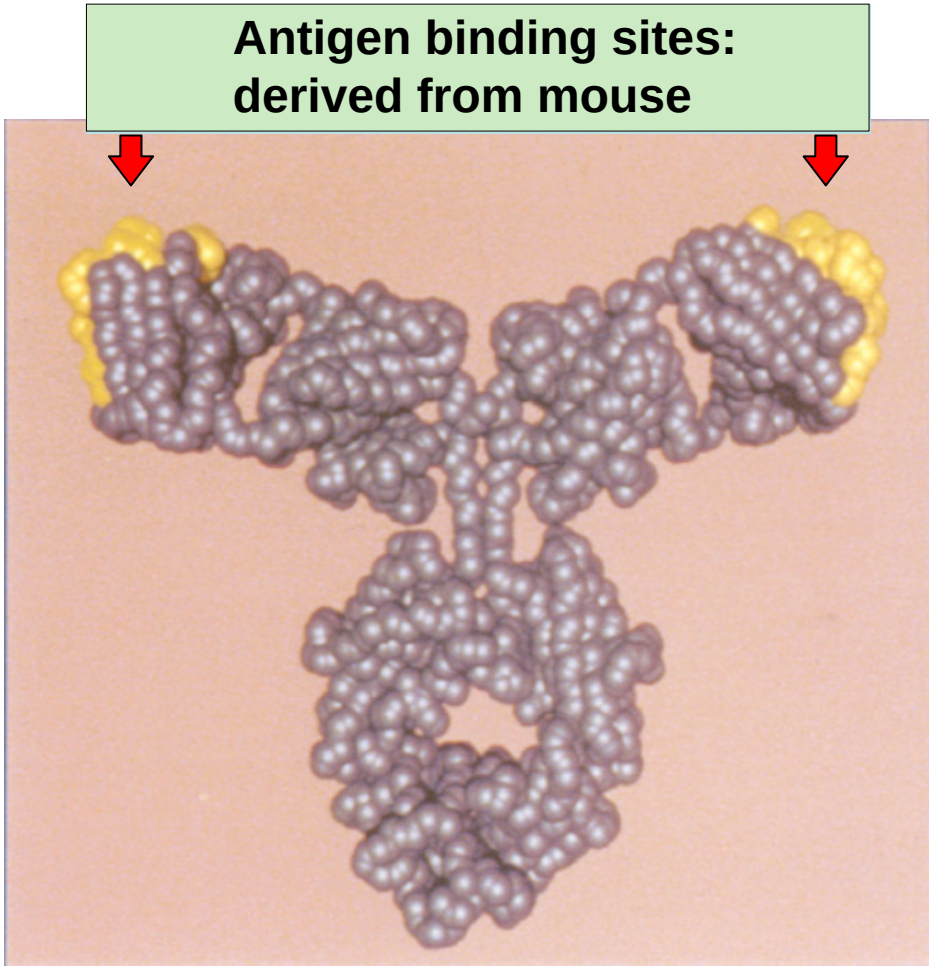
Herceptin
Anti-HER2 Humanized Monoclonal Antibody



- Target: HER2 receptor
- Molecular weight: 148,000
- 95% human IgG1-derived
  5% murine parent antibody-derived
- Antibody-dependent cell-mediated cytotoxicity (ADCC)

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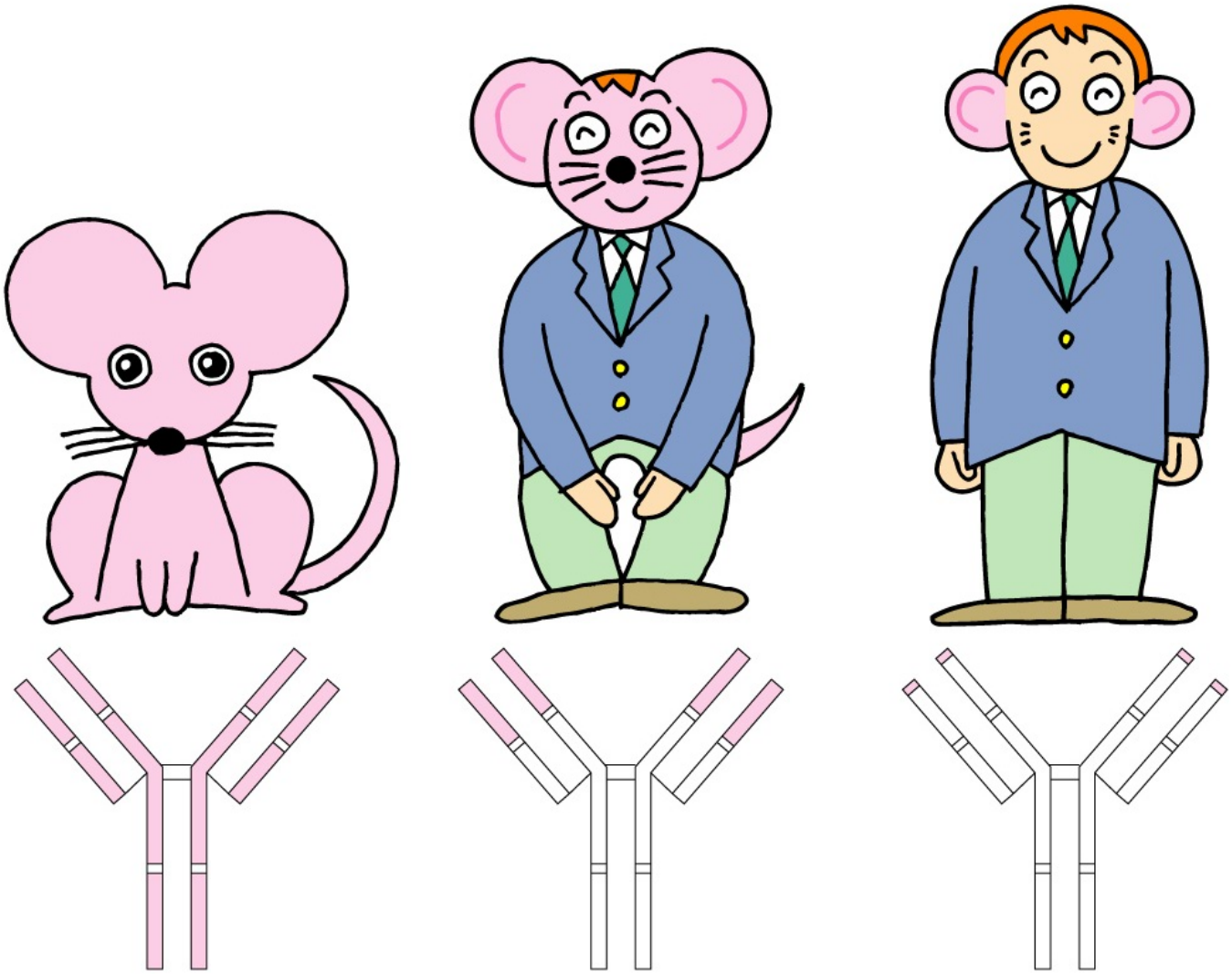
Differences in antibodies

Murine antibody **Chimeric antibody** **Humanized antibody**



Mouse-derived % **100%** **33%** **10%**

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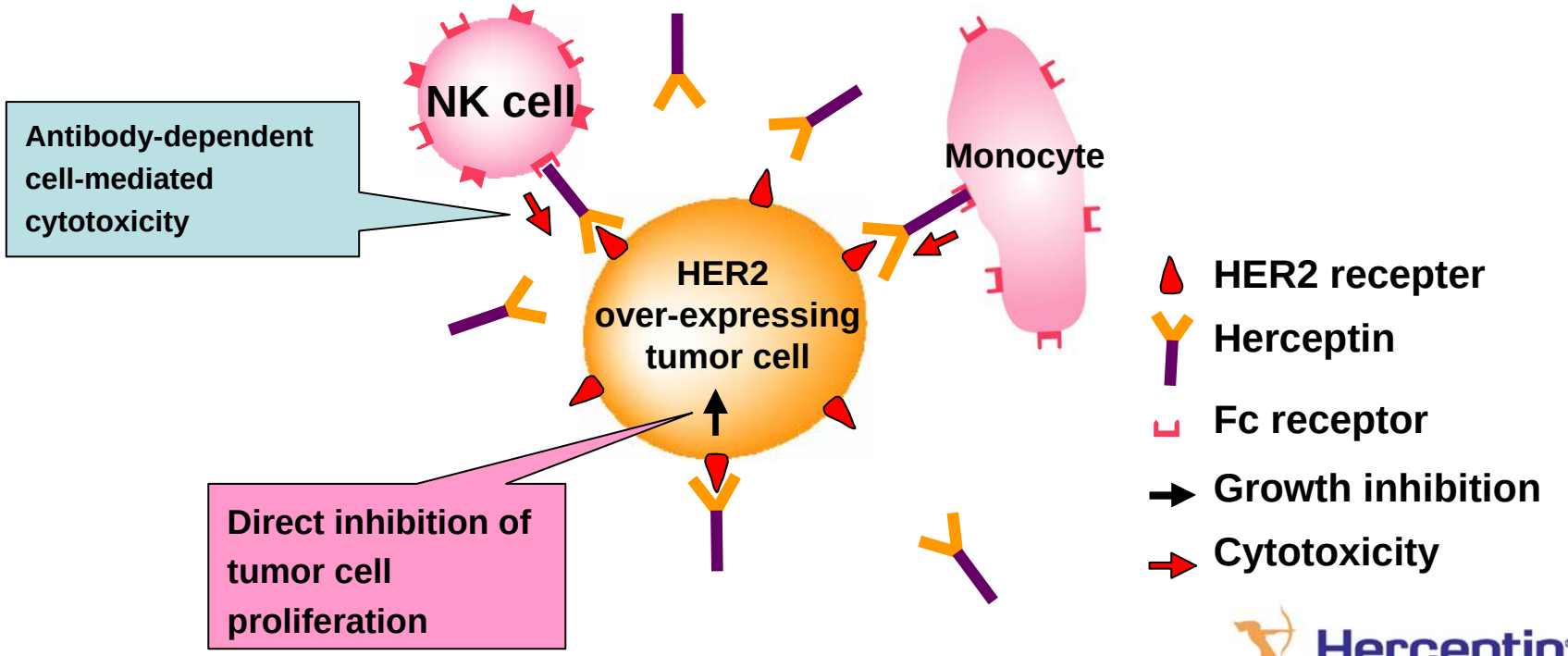
Mechanism of Action

- **Antibody-dependent cell-mediated cytotoxicity via Fc receptor on monocyte and NK cell**

  Induction of ADCC (Antibody- dependent cell-mediated cytotoxicity)

- **Direct inhibition of tumor cell proliferation through binding to HER2 receptor**

（Schematic view ）



Lewis GD, et al.：Cancer Immunol. Immunother, 37：255, 1993

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Product Characteristic

1 Standard therapy for HER2 positive breast cancer

- Herceptin is recommended by global and Japanese Guidelines as standard therapeutic agent for HER2 positive breast cancer.

2 Prolongation of survival

- In clinical trials involving patients with HER2 positive breast cancer, Herceptin has demonstrated significantly longer disease-free survival as well as overall survival.

3 Antibody with specific action on HER2

- Herceptin is the world's first humanized monoclonal antibody which is effective specifically for HER2 positive breast cancer with poor prognosis. This is a pioneer drug as molecular target medicine which specifically targets HER2 receptor.

4 Accumulated safety data

- Sufficient safety information since launch has been accumulated in Japan and global.

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Indications

- HER2 over-expressed metastatic breast cancer
- Adjuvant chemotherapy for HER2 over-expressed early breast cancer

<Precautions regarding indications>

1. HER2 overexpression tests should be conducted under a well-experienced pathologist or at a well equipped laboratory.
2. The efficacy and safety of Herceptin as a neoadjuvant therapy have not yet been established.

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Dosage and Administration

- In case of metastatic breast cancer in which HER2 over-expression was confirmed

  Usually for adults, an initial dose of 4 mg trastuzumab per kilogram body weight, and subsequent doses of 2 mg/kg, are administered at a week interval as a single intravenous drip infusion over at least 90 minutes.

- **In case of adjuvant chemotherapy in early breast cancer in which HER2 over-expression was confirmed**

  Usually for adults, an initial dose of 8 mg trastuzumab per kilogram body weight, and subsequent doses of 6 mg/kg, are administered at three week-intervals as a single intravenous drip infusion over at least 90 minutes.

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Dosage and Administration

1. **In case of metastatic breast cancer in which HER2 over-expression was confirmed**

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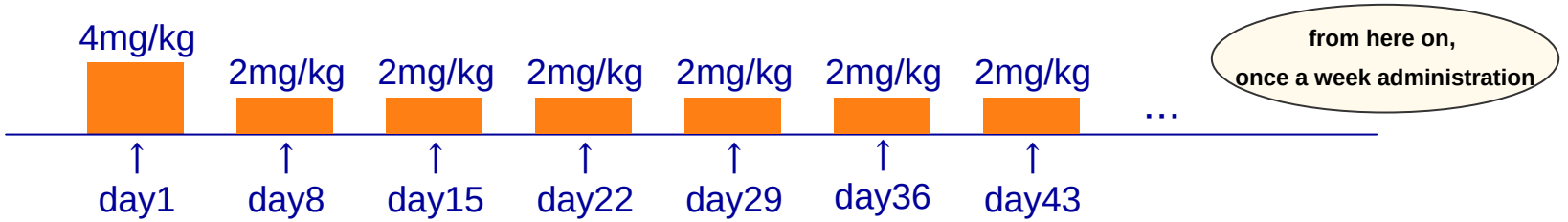
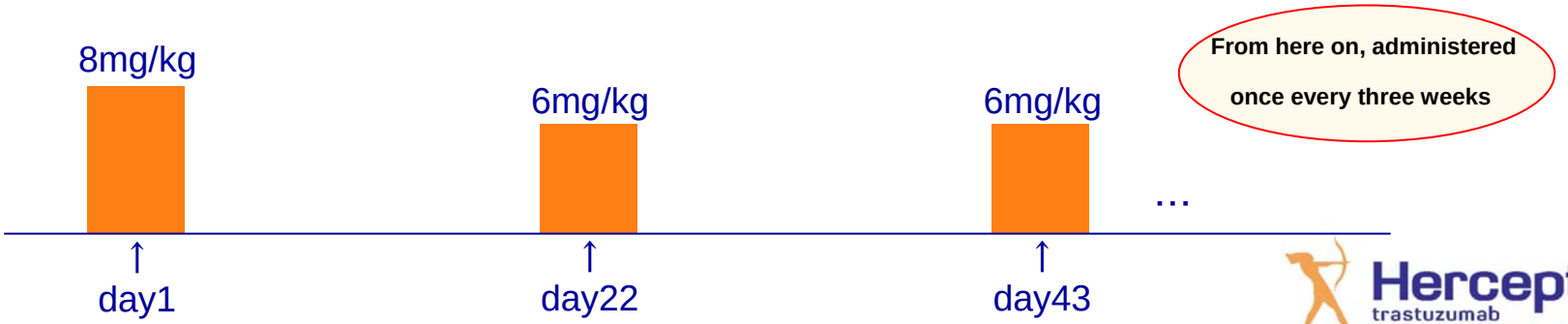


2. **In case of post-op adjuvant chemotherapy in early breast cancer in which HER2 over-expression was confirmed**

   Usually for adults, an initial dose of 8 mg trastuzumab per kilogram body weight, and subsequent doses of 6 mg/kg, are administered at three week-intervals as a single intravenous drip infusion over at least 90 minutes.



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Warnings

1. Anticancer chemotherapy involving Herceptin should be administered only to patients for whom treatment with Herceptin is judged to be appropriate, at medical institutions where effective emergency treatment can be provided, under the supervision of a physician with sufficient knowledge of and experience with cancer chemotherapy. In selecting eligible patients for Herceptin, close attention must be paid to the package insert of Herceptin. Furthermore, prior to the initiation of Herceptin administration, a full explanation should be given to the patient and/or his/her family about the efficacy of, and risks associated with Herceptin, and his/her/their informed consent should be obtained.

2.As it has been reported that serious cardiac disorder such as cardiac failure developed and resulted in fatal cases, the patient's cardiac function should be evaluated prior to the start of Herceptin therapy. Further, during Herceptin therapy, cardiac function (echocardiography, etc.) should be monitored as necessary and the patient's condition (including changes of left ventricular ejection fraction (LEVEF)) should be closely observed. In particular for the following patients, cardiac function (echocardiography, etc.) should be monitored frequently.

1)Patients receiving an anthracycline or with prior anthracycline exposure

2)Patients receiving radiation therapy to the thoracic region

3)Patients with cardiac failure symptoms

4)Patients with current or a history of coronary artery diseases (myocardial infarction, angina pectoris, etc.)

5)Patients with current or a history of hypertension

3. Infusion reactions often develop during or within 24 hours of the start of Herceptin therapy. It has been reported that of patients with such infusion reactions, some who presented serious adverse reactions such as anaphylactoid symptoms, pulmonary disorders, etc. (bronchospasm, severe blood pressure decrease, acute respiratory distress syndrome (ARDS), etc.) resulted in fatal cases. Since these adverse reactions are likely to become serious, particularly in patients with current or a history of dyspnoea at rest (due to lung metastasis, cardiovascular diseases, etc.), Herceptin should be carefully administered, while monitoring the patient's condition closely.

Important Precautions

(1) **Since serious cardiac disorders such as cardiac failure may occur, the patient's cardiac function must be monitored before initiation of Herceptin treatment. In addition, during therapy with Herceptin, cardiac function (echocardiography, etc.) should be monitored as necessary in accordance with the onset status, seriousness, etc. of the cardiac condition, the patient's condition (including changes of left ventricular ejection fraction (LEVF)) should be monitored closely, and whether to temporarily suspend, resume or discontinue therapy with Herceptin should be assessed.**

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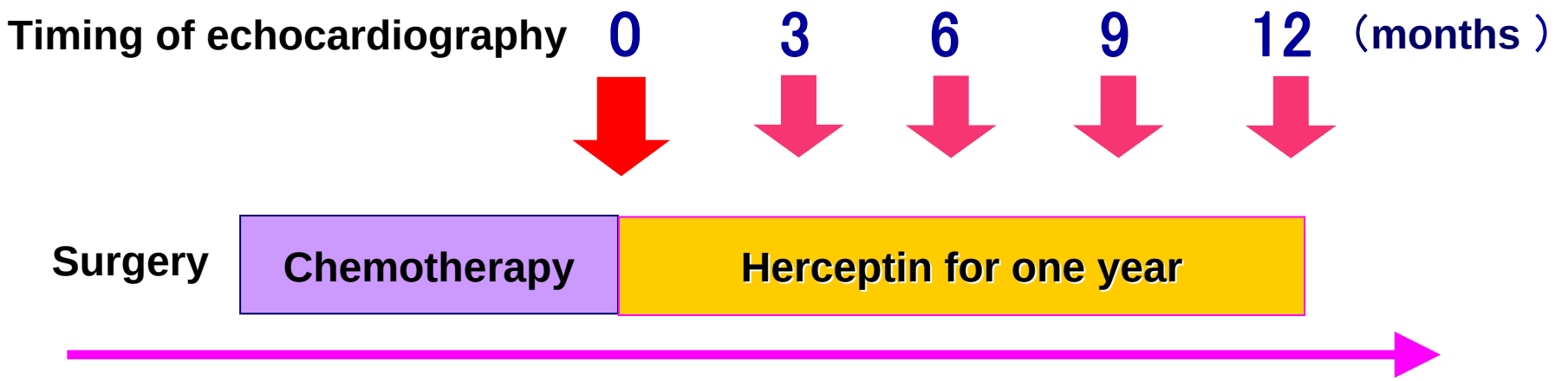
Cardiac function monitoring



While the patient is on Herceptin;

- Method and schedule for proper assessment of cardiac function have yet to be established. However, the assessment at 3-months intervals is recommended as the cardiac function assessment schedule as employed in the clinical trials.

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