

Pharmacoeconomics of Trastuzumab (Herceptin[®])

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Although this presentation includes information regarding pharmaceuticals (including products under development), the information is not intended as any advertisement and/or medical advice.

Background of the need for evaluating efficiency of medical practice

Market failure in medical practice

Need for more efficient allocation of resources

Tight medical financial resources

More effective use of public/insurers' funds

EBM(Evidence Based Medicine)

clinical evidence→economic evidence

Evaluation of efficiency

Which is more efficient, Car A or Car B?

When fully fueled

	Possible distance to be covered	GAS	Fuel efficiency
Car A	500km /	40 ℓ	= 12.5km/ℓ
Car B	600km /	50 ℓ	= 12.0 km/ℓ

Elements of economic evaluation

Economic evaluation of Medical technology

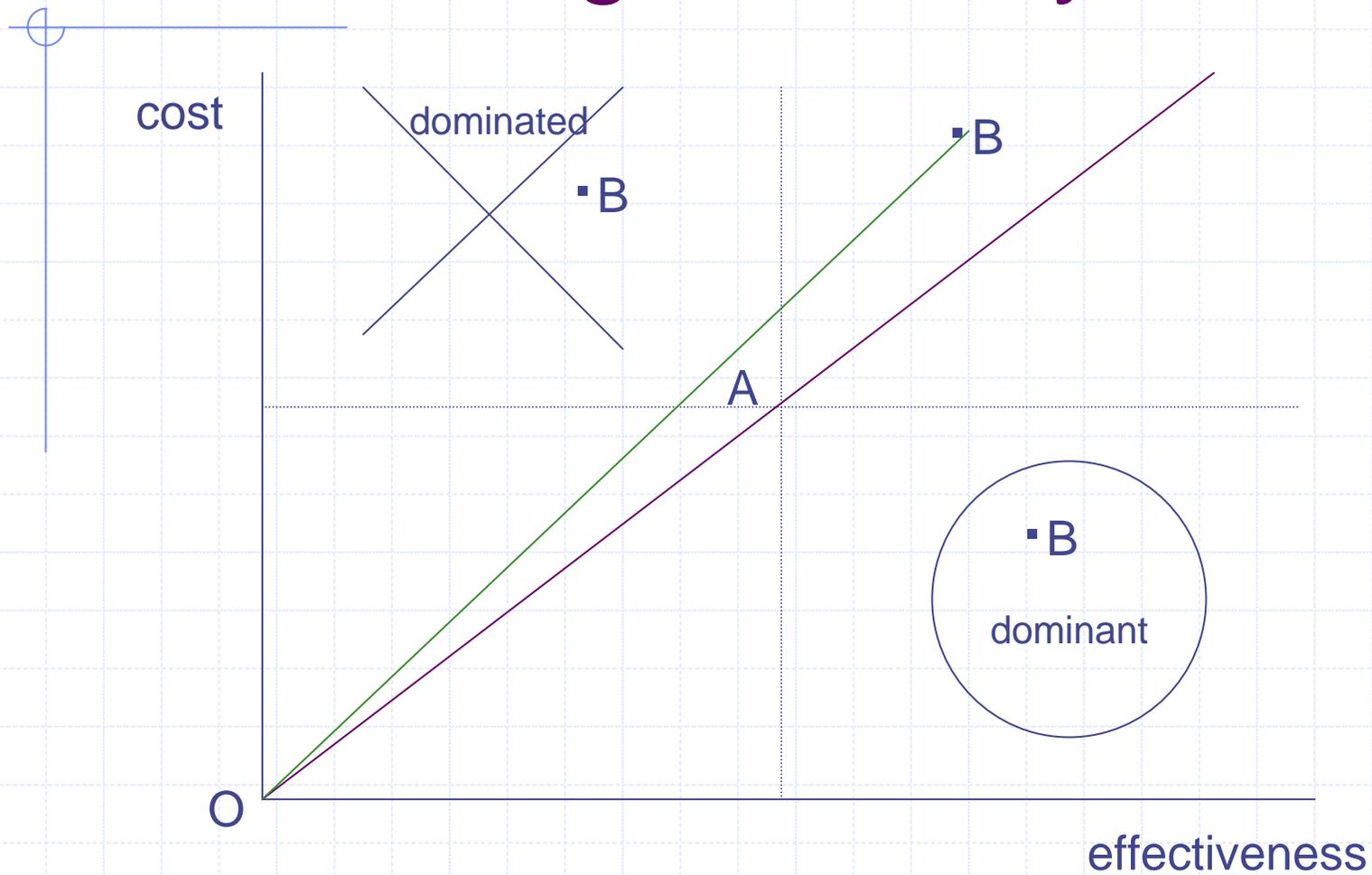
Are both input and output studied?

Are more than
two programs
compared?

		NO		YES
		Output only studied	Input only studied	
NO	PARTIAL EVALUATION	Outcome description	Cost description	PARTIAL EVALUATION Cost-outcome description
		YES	Efficacy or Effectiveness evaluation	Cost analysis

(Drummond et al., 1997)

Determining efficiency



In case of pharmaceutical products

Which is more efficient, existing drug (A) or new drug (B)?

Condition: Treatment period is 1 year for both drugs

Annual cost for drug A: ¥1million/ patient

drug B: ¥1.5million/ patient

Outcome is survival after 5 years

Out of 100 patients drug A : 60 patients survived

drug B : 80 patients survived

In case of pharmaceutical products

Which is more efficient, existing drug (A) or new drug (B)?

	cost	effectiveness	cost /effectiveness ratio
Drug A	¥100 million	/ 60 patients	= ¥1.67million/Life saved
Drug B	¥150 million	/ 80 patients	= ¥1.88 million/Life saved

- Should drug A be used as in the past since drug B is less efficient?
- Should drug B be used if effectiveness is 95 patients (CE ratio = ¥1.58 million/LS)?
 - More effective drug is naturally wanted in medicine, But What is important is whether there is any value in paying additional ¥50 million

CER and ICER

A: Standard drug ,B: New drug

Cost Effectiveness Ratio (CER)

$$= \frac{\text{cost(B)}}{\text{effectiveness(B)}}$$

Incremental Cost Effectiveness Ratio (ICER)

$$= \frac{\text{cost(B)} - \text{cost(A)}}{\text{effectiveness(B)} - \text{effectiveness(A)}}$$

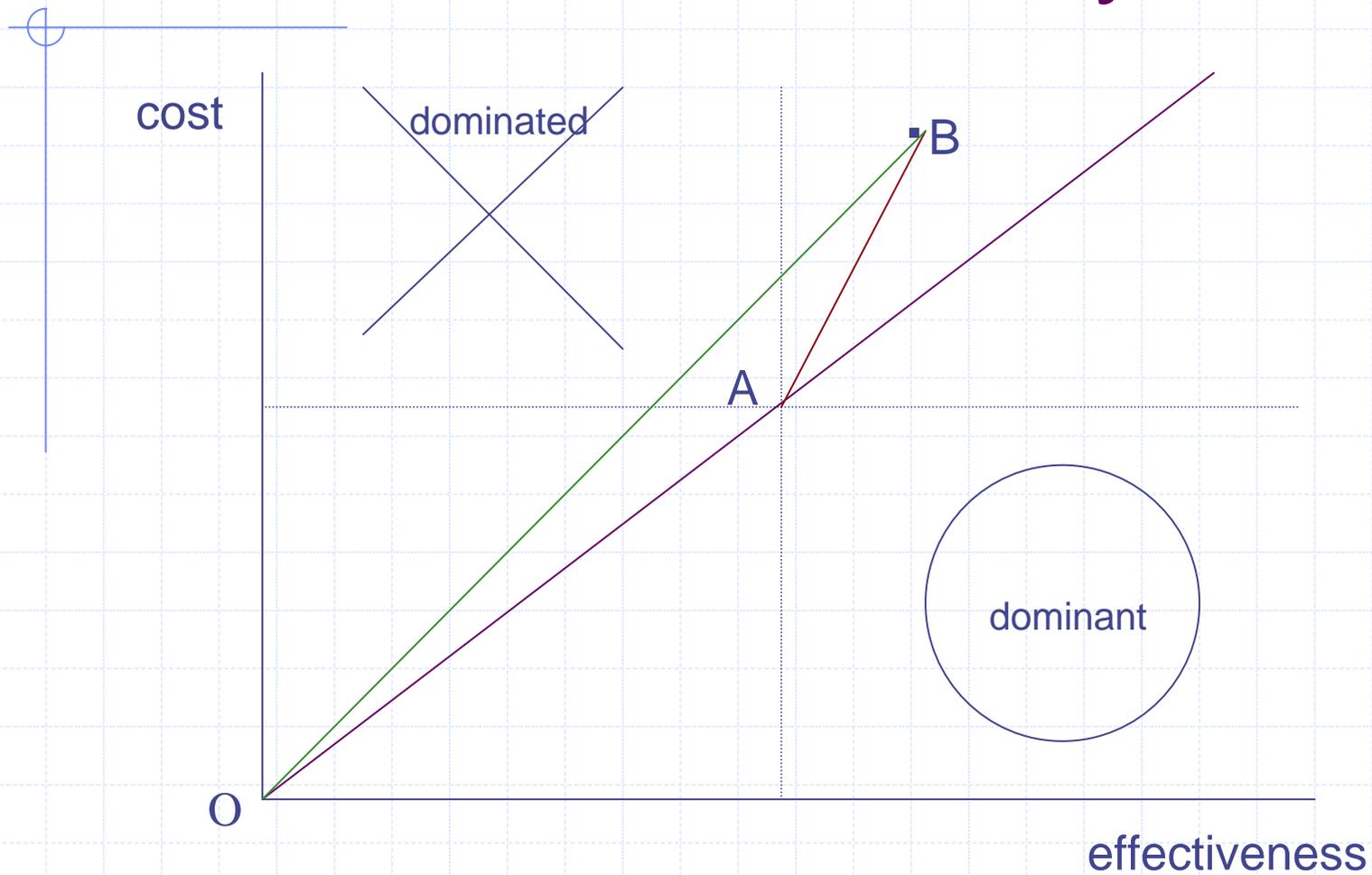
In case of pharmaceutical products

Which is more efficient, existing drug (A) or new drug (B)?

	Cost	Effectiveness	Cost Effectiveness Ratio
drug A	¥100 million	/ 60 patients	= ¥1.67million / Life Saved
drug B	¥150 million	/ 80 patients	= ¥1.88million / Life Saved

$$\text{ICER} = \frac{\text{¥150 million} - \text{¥100 million}}{80 \text{ patients} - 60 \text{ patients}} = \text{¥2.5 million / Life Saved}$$

Evaluation of efficiency



Methods of pharmacoeconomics

- Cost minimization analysis
- Cost effectiveness analysis
- Cost utility analysis
- Cost benefit analysis



Ways of thinking on cost is same,
ways of measuring results is different

CEA (Cost Effectiveness Analysis)

Life Years Gained or other physical scale (blood pressure, etc) are used to evaluate effectiveness.



Method most generally used but necessary to select one scale to evaluate effectiveness.

CUA (Cost utility analysis)

Utility values such as QALY (Quality Adjusted Life Years), considering both Life Years and QOL(Quality of Life) are used.



Enables comparison of results of evaluation of various drugs, medical practices and preventive activities. How to evaluate QOL is an issue.

QALY calculation

$$QALYs = \sum_H Q_H \times L_H$$

H : Health status

Q_H : Quality Weight (Full health=1, Dead=0) in a healthy state

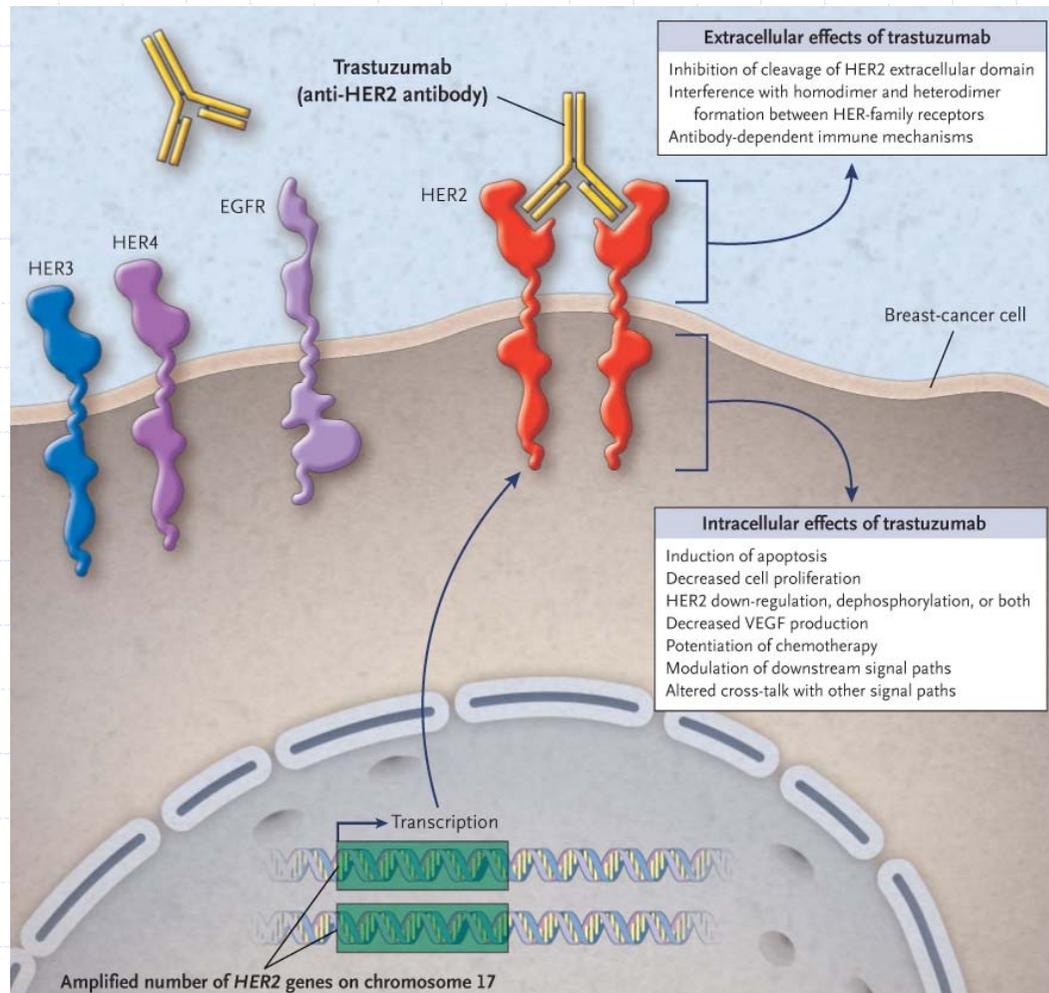
L_H : Years of survival in a healthy state

1 QALY: 1 Life Year in a complete healthy state

The model-based cost-effectiveness analysis of 1-year adjuvant trastuzumab(Herceptin®) treatment : based on 2-year follow-up HERA trial data

**Shiroiwa T, Fukuda T, Shimosuma K, Ohashi Y, Tsutani K.
The model-based cost-effectiveness analysis of 1-year adjuvant
trastuzumab treatment: based on 2-year follow-up HERA trial
data.
Breast Cancer Res Treat 2007**

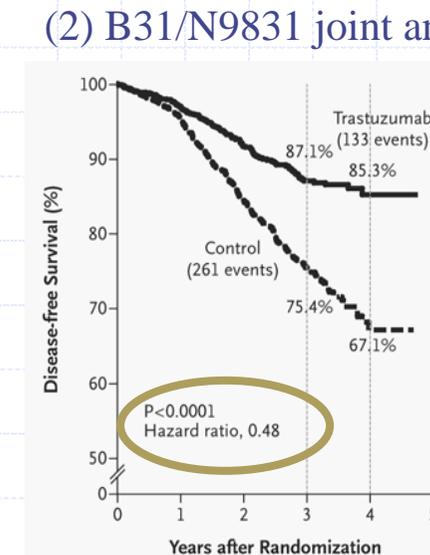
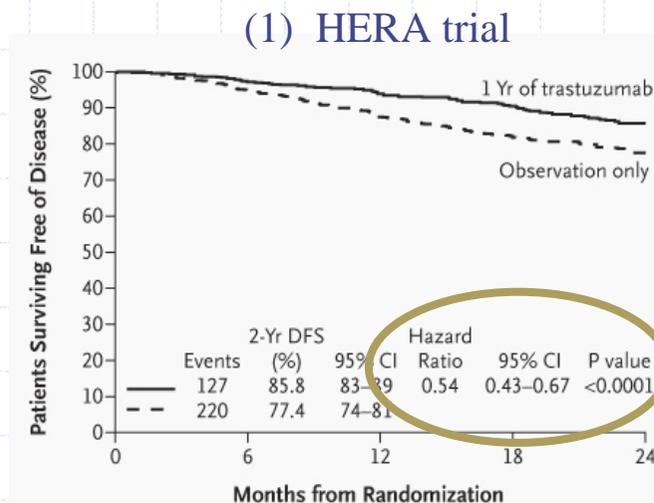
Background



- Trastuzumab is a monoclonal antibody that binds specifically to HER2 protein expressed on cellular surface.
- Cell proliferation is inhibited by blocking intracellular signal transduction.
- Approved in Japan for metastatic breast cancer in 2001.
- Indicated only for patients over-expressing HER2 protein.

Evidence for adjuvant therapy in Breast Cancer

- ◆ Results of 3 RCT verifying the efficacy of Trastuzumab as adjuvant setting were reported at ASCOT in 2005.



- ◆ “not evolutionary but revolutionary” (NEJM 2005; 353: 1734-1736)

Drug Cost

Initial dose of 8mg/kg and following dose of 6mg/kg from 2nd treatment every 3 weeks for 1 year

If the bodyweight is 50-60kg, total dosage is 300mg~360mg



¥178,220
for one
treatment

Drug Cost is
¥3,251.683
for one year

Problems

- ◆ It is a revolutionary treatment reducing relapse to only half of the patients.
- ◆ But cost for treatment is not cheap.
- ◆ However, if there is effectiveness gained from the price, it is acceptable.
- ◆ Cost of adjuvant treatment is like an initial investment. If metastasis / relapse can be prevented and save medical expenses, which is better?



Cost effectiveness analysis including metastasis and relapse should be made to see if the treatment is worth the expensive initial investment.

Objectives

- ◆ Evaluate cost effectiveness of Trastuzumab by calculating CER of HER-2 positive breast cancer patients treated with the drug against control arm.
- ◆ (a) Trastuzumab 1-year treatment arm
 - after standard post(pre)-operative chemotherapy, treated with initial dose of Trastuzumab 8mg/kg and 6mg/kg from 2nd treatment, every 3 weeks for 1 year
- ◆ (b) Observation arm
 - treated with only standard post(pre-)operative chemotherapy

Outline of study

◆ CEA (cost-effectiveness analysis)

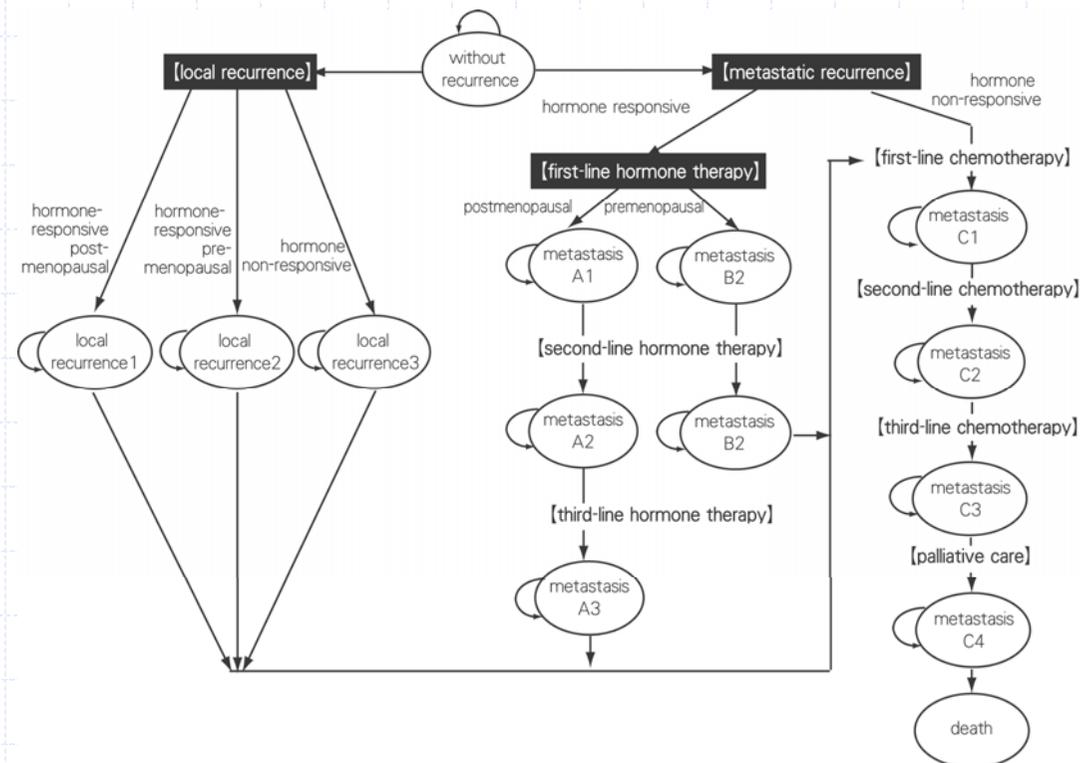
◆ ICER (incremental cost-effectiveness ratio) indicating results.

$$\text{ICER} = \frac{C_t - C_c}{E_t - E_c} = \frac{\Delta C (\text{incremental cost})}{\Delta E (\text{incremental effectiveness})}$$

◆ Unit for ICER is ¥/LYG (life-year gained)

Model for treatment process

- ◆ Markov model was developed to analyze process after chemotherapy. Time horizon is 50 years, 600 cycles. (1 cycle=1month)



Data source

- ◆ HERA trial (the Herceptin adjuvant trial, 2007) was used to evaluate efficacy (median follow-up time is 2 years). Hazard ratio for relapse was 0.64.
- ◆ Standard treatment process was developed to calculate cost on fee for yield, using Medical Fee Table and Standard Drug Price of FY 2004. Only direct cost was included and indirect cost (labor loss, etc) was excluded.

Main hypothesis

- ◆ How long the effect of Trastuzumab lasts is undetermined. So ICER was calculated on 3 scenarios, assuming its effect to last for 2 years (conservative), 5 years (base case) and 10 years (optimistic).
- ◆ Average bodyweight of Japanese women, 50-60kg, was used as standard, but bodyweight of 60-70kg was also estimated.
- ◆ As long-term prognosis of breast cancer, relapse rate after 5 years was estimated to be 0.5 times that of up to 5 years, from results of EBCTCG meta-analysis (2005).

Results

	C	E
Observation arm	¥7,900,000	12.46
Trastuzumab arm (conservative)	¥11,500,000	13.06
Trastuzumab arm (standard)	¥11,200,000	13.70
Trastuzumab arm (optimistic)	¥10,900,000	14.10
	$\Delta C / \Delta E$ (ICER)	
Observation arm		
Trastuzumab arm (conservative)	¥6,000,000	
Trastuzumab arm (standard)	¥2,600,000	
Trastuzumab arm (optimistic)	¥1,800,000	

Sensitivity analysis

	weight class		
	~50 kg	50 kg~60 kg	60 kg~75 kg
2 years (conservative)	¥5,100,000	¥6,000,000	¥7,400,000
5 years (standard)	¥2,200,000	¥2,600,000	¥3,300,000
10 years (optimistic)	¥1,500,000	¥1,800,000	¥2,300,000

Discussion

- ◆ **NICE in UK refers to recommended threshold value of £20,000 to £30,000 (about 5 to 7 million Yen) per 1 QALY.**
- ◆ **Reference in US is \$50,000 to \$100,000 (about 50 to 10 million Yen) per 1 QALY.**

Results of analysis in different countries

country	trial	ICER	reference
UK	HERA	£18,000/QALY	NICE technology appraisal guidance 107
Italy	joint analysis	€14,861/QALY	JCO 2007; 25: 625-33
US	joint analysis	\$18,970/QALY	JCO 2007; 25: 625-33
US	joint analysis	\$39,982/QALY	JCO 2007; 25: 634-41
Australia	HERA+joint	\$A22,793/QALY	Pharmacoeconomics 2007; 25: 429-442

NICE in UK recommends Trastuzumab adjuvant in Guidance issued in August, 2006.

NICE

National Institute for Health and Clinical Excellence

- Established in 1999 as Special Health Authority to improve the standard of clinical medicine and to promote effective use of resources.

- Technology appraisals

Economics of pharmaceutical products, medical technology, surgical method, health promotion, etc. are evaluated and recommendation is given to NHS whether or not to be included it in the benefit. Health authority is obliged to add to grant range based on recommendation, from 2002.

- Clinical guidelines

Treatment considered appropriate for certain diseases and symptoms are indicated.

Trastuzumab for the adjuvant treatment of early-stage HER2-positive breast cancer

NICE technology appraisal guidance 107, August 2006

1 Guidance

- 1.1 Trastuzumab, given at 3-week intervals for 1 year or until disease recurrence (whichever is the shorter period), is recommended as a treatment option for women with early-stage HER2-positive breast cancer following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable).

(<http://www.nice.org.uk/nicemedia/pdf/TA107guidance.pdf>)

3.6

The evidence review group then developed a number of scenarios that reflected alternative assumptions. Using the manufacturer's model, they altered the proportion of women receiving trastuzumab in the metastatic setting to better reflect the advice on likely use in clinical practice and shortened the duration of benefit obtained from trastuzumab. This resulted in an estimate of approximately £18,000 per additional QALY gained for the 3-weekly regimen. Other scenarios modelled on this estimate gave incremental costs per QALY gained ranging from £16,000 to £33,000.

(<http://www.nice.org.uk/nicemedia/pdf/TA107guidance.pdf>)

What is high-cost medical care?

- ◆ Medical fees become so expensive when hospitalization or treatment is prolonged due to serious disease.
- ◆ To decrease burden on household economy, High-Cost Medical Care System provides refund on health care expenditure exceeding certain level of amount (Maximum personal burdens).
- ◆ Differences from Special Health Care Expenditure and Inpatient Meal Expenses are not funded.

High-cost medical care system

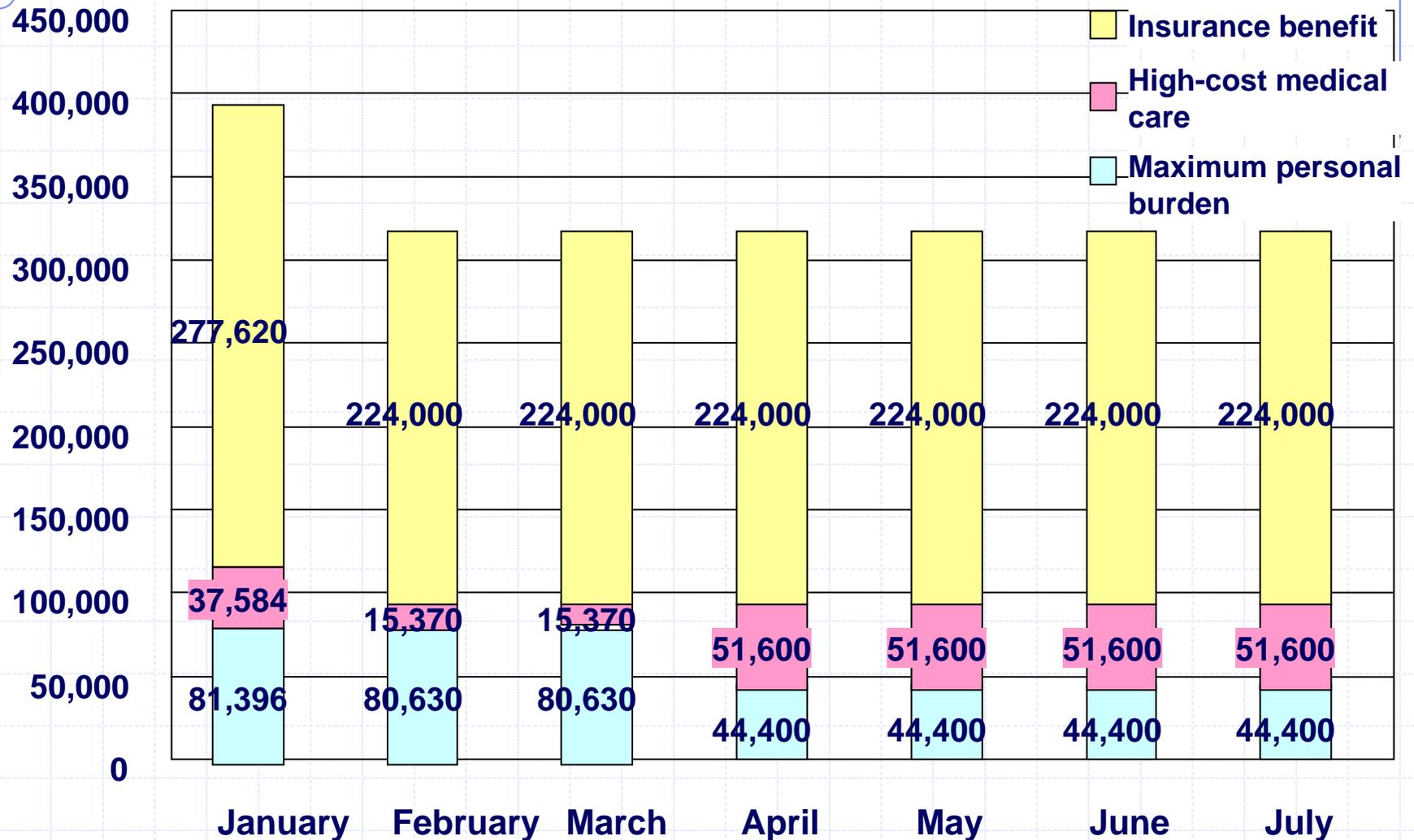
Maximum personal burdens (under 70 years old)

Category		
High income earners	Object	Standard income: \leq ¥530,000
	Ordinary	150,000+ (Medical fees – 500,000) x1%
	Frequent application	83,400
General Income earners	Ordinary	80,100+ (Medical fees-267,000) x1%
	Frequent application	44,400
Low income earners	Ordinary	35.400
	Frequent application	24.600

- Note
- “General” in this category are those insured other than high and low income earners.
 - Low income earners are the insured of households protected under Daily Life Security Law and households exempt from municipal tax.
 - “Frequent qualification of expenditures” means more than 4 times.

“Frequent qualification of expenditures”

(Case of Herceptin hospitalization → outpatient treatment)
 = if monthly income are less than ¥530,000



Conclusion

Although use of Trastuzumab as adjuvant setting requires additional budget, the treatment is considered economically superior in the view of cost effectiveness perspective.

On the other hand, Patients can reduce their burden of medical cost by making use of High-Cost Medical Care System.

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