Electronic Supplementary Material

Real-world comparative analysis of trastuzumab originator and biosimilars: Safety, efficacy, and cost-effectiveness

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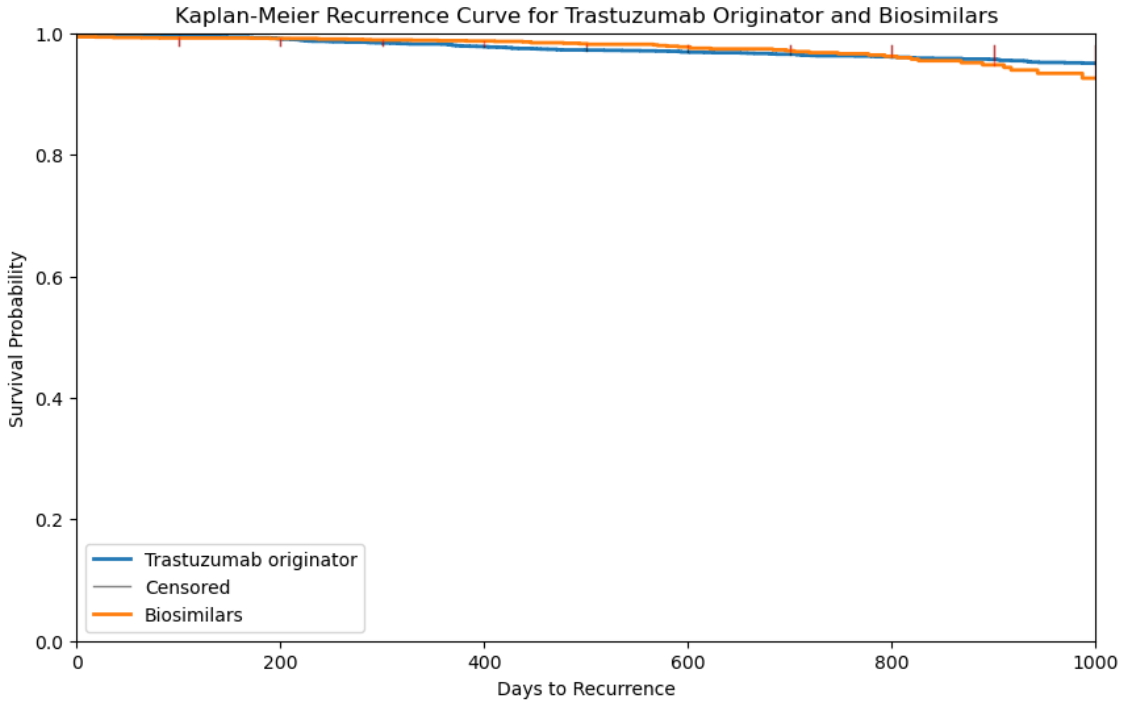
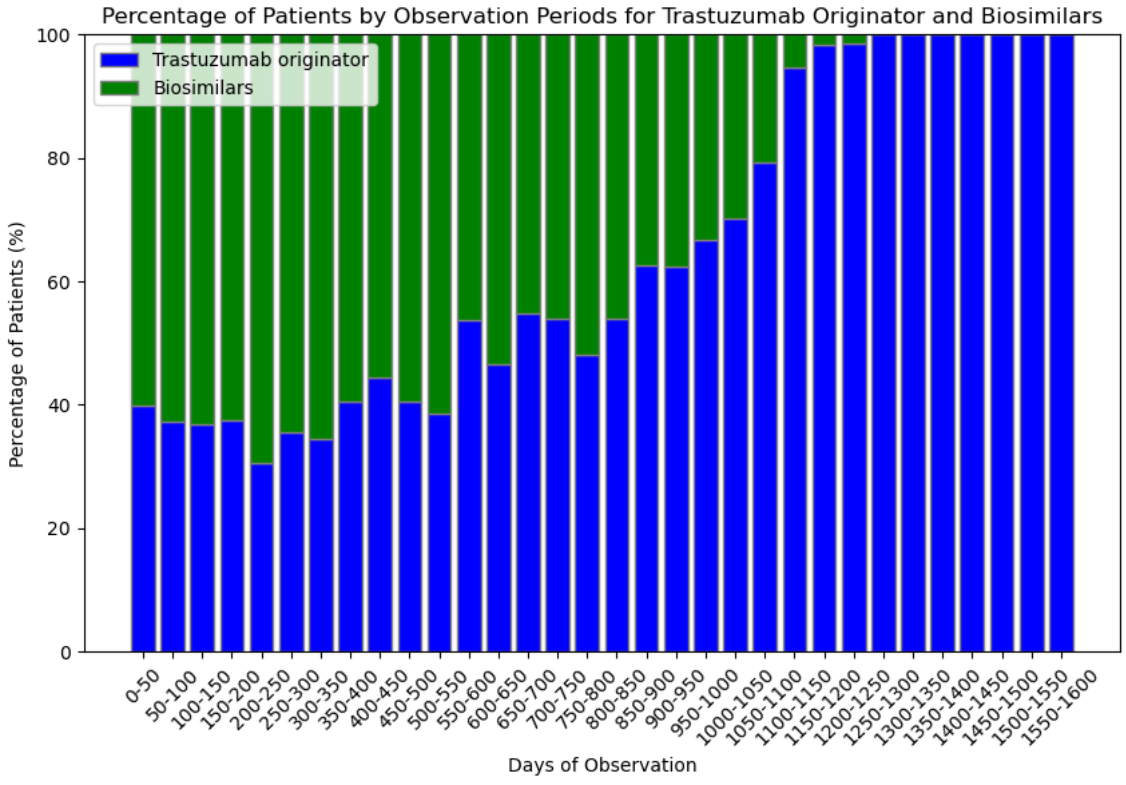
Supplementary Figure 1 (A)

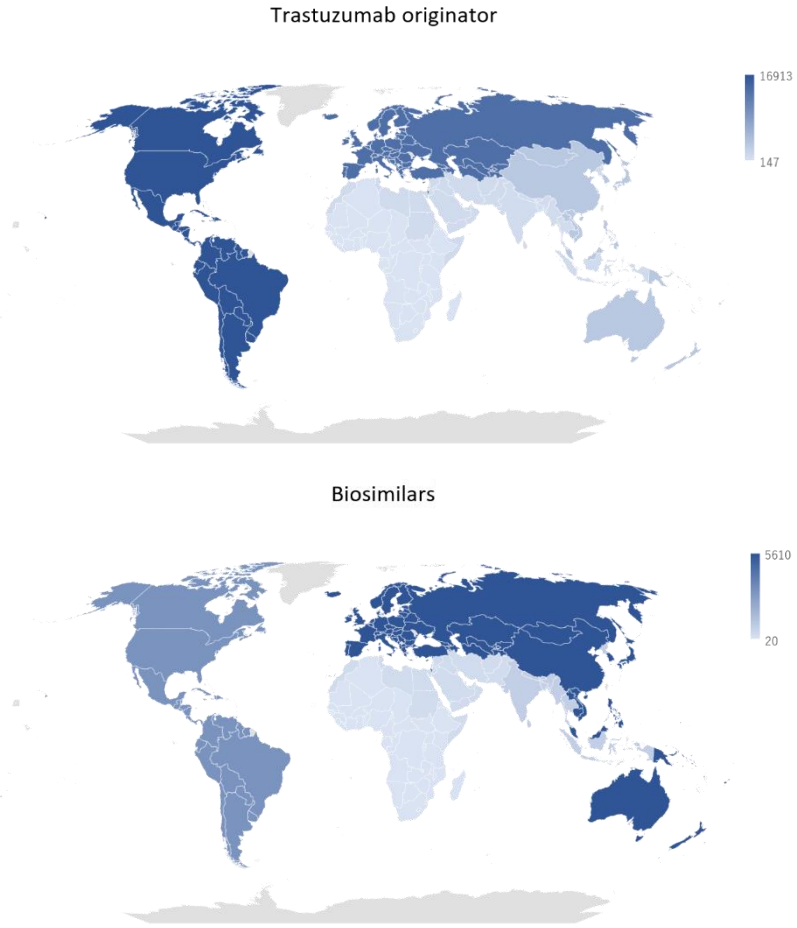


Supplementary Figure 1 (B)



Supplementary Figure 1. Analysis of Differences in Observation Periods.
(A) Recurrence curves for the trastuzumab originator and biosimilars groups, with a hazard ratio of 1.07 (95% CI: 0.79-1.44, p = 0.68), indicating no statistically significant difference. **(B)** Patient observation periods shown as percentages, with the trastuzumab originator group having a longer observation period compared to the biosimilars group.

Supplementary Figure 2



Supplementary Figure 2. WHO Region-Based Map of Report Numbers. Color-coded maps representing the number of reports for trastuzumab originator (left) and biosimilars (right). Darker colors indicate higher numbers of reports. Data were collected from WHO's VigiBase up to December 2021. **Regions include:** African Region, Region of the Americas, Eastern Mediterranean Region, European Region, South-East Asia Region, and Western Pacific Region.

Supplementary Table 1

Number of Subjects

	Trastuzumab originator (N)	Biosimilars (N)
Infusion reactions	1,331	298
Heart failure	11,115	2,767
BNP	183	104
Total bilirubin	1,333	364
AST	1,341	364
ALT	1,345	366

Supplementary Table 1. Number of Subjects Analyzed. Number of subjects analyzed in the trastuzumab originator and biosimilars groups for each adverse event, including B-type Natriuretic Peptide (BNP), Aspartate Aminotransferase (AST), and Alanine Aminotransferase (ALT).

Supplementary Table 2

Patient characteristics since 2018

	Trastuzumab originator N=3,779 (%)	Biosimilars N=2,767 (%)	P-value
Female	3,766 (99.7)	2,761 (99.8)	0.48
Male	13 (1.7)	6 (1.2)	
Median age (range)	60.0 (22-95)	59.0 (23-90)	0.09
NAC	1,321 (35.0)	1,078 (39.0)	**0.001**
Adjuvant	2,458 (65.0)	1,689 (61.0)	
Anthracycline-Taxane	1,987 (52.6)	1,454 (52.5)	0.09
Taxane	1,177 (31.1)	894 (32.2)	
Anti-HER2 monotherapy	473 (12.5)	298 (10.8)	
Others	142 (37.6)	121 (43.7)	
With Pertuzumab	2,013 (53.3)	1,692 (61.1)	**1.98e-10**
Without Pertuzumab	1,766 (46.7)	1,075 (38.9)	

Supplementary Table 2. Patient Characteristics. Characteristics of cases since August 2018 are presented.

Supplymentary Table 3

(A) Infusion reactions

	Trastuzumab originator N=1,331 (%)	Biosimilars N=298 (%)	P-value
Dexchlorpheniramine	26 (2.0)	10 (3.3)	0.19
Hydroxyzine	1 (0.1)	1 (0.3)	0.33
Hydrocortisone	18 (1.4)	5 (1.7)	0.59
Ropivacaine	10 (0.8)	1 (0.3)	0.70
Acetaminophen	5 (0.4)	4 (1.3)	0.06
Any of the above	55 (4.1)	17 (5.7)	0.28

(B) Heart Failure

	Trastuzumab originator N=11,115 (%)	Biosimilars N=2,767 (%)	P-value
Hospitalized for heart failure	43 (0.39)	15 (0.54)	0.25
Diagnosis of heart failure	601 (5.4)	153 (5.5)	0.81
	Trastuzumab N=183 (%)	Biosimilars N=104 (%)	P-value
BNP 100 pg/ml or higher	21 (11.5)	3 (2.9)	**0.01**

(C) Liver Dysfunction

	Trastuzumab originator	Biosimilars	P-value
Total bilirubin	N=1,333	N=364	
Grade1	45	7	
Grade2	11	2	0.75
AST	N=1,341	N=364	
Grade1	459	129	
Grade2	24	1	
Grade3	10	2	1.0000
ALT	N=1,345	N=366	
Grade1	523	152	
Grade2	70	9	
Grade3	28	1	**0.01**

(D) Administration Frequency and Cost

	Trastuzumab originator N=10926	Biosimilars N=2761	P-value
Average number of administrations (range)	16.8 (1-30)	13.8 (1-30)	**8.18e-142**
Average amount	1,897,206 JPY	769,583 JPY	**p < 0.0001**
Amount per administration	112,783 JPY	55,806 JPY	**p < 0.0001**

Supplementary Table 3. Adverse Events and Administration Details. (A) Infusion Reactions: Includes cases receiving monotherapy with either trastuzumab originator or biosimilars, excluding concurrent use of other cytotoxic agents. No significant differences observed. **(B) Heart Failure:** Includes cases with a history of hospitalization and diagnosed heart failure. No significant differences between the groups, though BNP (B-type Natriuretic Peptide) levels above 100 pg/mL were more prevalent in the trastuzumab originator group. **(C) Liver Function:** Classified according to CTCAE v5.0 criteria. No significant differences in total bilirubin and Aspartate Aminotransferase (AST) levels between the groups. Grade 3 or higher adverse events for Alanine Aminotransferase (ALT) were observed in the trastuzumab originator group. **(D) Average Number of Administrations and Cost:** Details on average administrations and costs during the perioperative period. Biosimilars showed significantly fewer doses (13.8 vs. 16.8), lower total costs (769,583 JPY vs. 1,897,206 JPY), and lower cost per administration (55,806 JPY vs. 112,783 JPY) compared to the originator.

Supplementary Table 4

(A) Heart Failure with Pertuzumab

	Trastuzumab originator with Pertuzumab N=2640 (%)	Biosimilars with Pertuzumab N= 1692 (%)	P-value
Hospitalized for heart failure	30 (1.1)	14 (0.8)	0.36
Diagnosis of heart failure	193 (7.3)	97 (5.7)	**0.046**
	Trastuzumab originator with Pertuzumab N=85 (%)	Biosimilars with Pertuzumab N＝69 (%)	P-value
BNP 100 pg/ml or higher	10 (11.8)	1 (1.4)	**0.023**

(B) Liver Dysfunction with Pertuzumab

	Trastuzumab originator with Pertuzumab	Biosimilars with Pertuzumab	P-value
Total bilirubin	N=275	N=225	
Grade1	9	6	
Grade2	4	2	0.70
AST	N=276	N=226	
Grade1	103	143	
Grade2	8	0	
Grade3	1	2	0.12
ALT	N=277	N=226	
Grade1	107	95	
Grade2	15	6	
Grade3	7	1	**0.02**

Supplementary Table 4. Adverse Events with Pertuzumab. (A) Heart Failure: Cases with a history of hospitalization showed no significant differences between the groups. Diagnosed heart failure and BNP levels above 100 pg/mL were more prevalent in the trastuzumab originator group. **(B) Liver Function:** Classified according to CTCAE v5.0 criteria. No significant differences in total bilirubin and Aspartate Aminotransferase (AST) levels between the groups. Grade 3 or higher adverse events for Alanine Aminotransferase (ALT) were observed in the trastuzumab originator group.

Supplementary Table 5.

Patient Distribution from VigiBase by Gender, Age, and Reported Year.

	Trastuzumab originator N=36,209 (%)	Biosimilars N=15,531 (%)
Reported year		
2024	36,209	15,531
2023	33,591	12,188
2022	30,964	10,322
2021	28,140	7,261
2020	24,579	4,422
2019	20,647	2,178
2018	16,490	203
Gender		
Male	1,525 (4.2)	862 (5.6)
Female	31,542 (87.1)	13,072 (84.2)
Unknown	3,142 (8.7)	1,597 (10.3)
Age		
< 45 years	4,498 (12.4)	2,130 (13.7)
=> 45 years	20,010 (55.3)	9,357 (60.2)
Unknown	11,701 (32.3)	4,044 (26)