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Efficacy and safety of biosimilar trastuzumab (CT-P6) in routine clinical practice in the Republic of Korea: a real-world post-marketing surveillance study

Min Ho Park [a], Jae Hong Seo [b], Jung Ho Park [c], Min-Ki Seong [d], Keon Uk Park [e], Min Kyoon Kim [f], Myungchul Chang [g], Su-Jin Koh [h], Moon Hee Lee [i], Seung Taek Lim [j], Young Bum Yoo [k], So Yeon Oh [l], Sung Hyun Kim [m], Keum Young Ahn [m], Tae Hong Park [m], Hana Ju [m], Eric Hyungseok Baek [m], Sinhye Kim [m], Nahyun Kim [m], Eunkyung Lee [m] and Tae Hyun Kim [n]

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ABSTRACT

Background: The trastuzumab biosimilar CT-P6 is approved for human epidermal growth factor receptor 2 (HER2)–positive early breast cancer (EBC), metastatic breast cancer (MBC), and metastatic gastric cancer (MGC). The objective of this post-marketing surveillance (PMS) study was to evaluate the real-world safety and effectiveness of CT-P6 in patients with HER2-positive cancers.

Research design and methods: This open-label, observational, prospective, PMS study collected data via investigator surveys from 35 centers in the Republic of Korea (5 October 2018–4 October 2022). Eligible patients with HER2-positive EBC, MBC, or MGC started CT-P6 treatment during routine clinical practice, followed by 1-year observation. Evaluations included adverse events (AEs), adverse drug reactions (ADRs), and effectiveness.

Results: Safety was analyzed in 642 patients (494 EBC, 94 MBC, 54 MGC). Overall, 325 (50.6%) patients experienced 1316 AEs, and 550 ADRs occurred in 199 (31.0%) patients. Unexpected ADRs occurred in 62 (9.7%) patients. Unexpected ADRs and ADRs of special interest did not raise any new safety signals. Among trastuzumab-naïve patients, 34/106 (32.1%) with EBC achieved pathological complete response; 30/74 (40.5%) MBC and 24/49 (49.0%) MGC patients achieved complete or partial response.

Conclusions: In a real-world setting, CT-P6 demonstrated safety and efficacy findings consistent with previous CT-P6 studies.

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Anti-HER2; biosimilar; CT-P6; human epidermal growth receptor 2; post-marketing surveillance; trastuzumab

1. Introduction

Trastuzumab, a humanized anti-human epidermal growth factor receptor 2 (HER2) monoclonal antibody, received regulatory approval in 1998, and has since transformed the treatment of patients with HER2-positive cancers [1,2]. In clinical trials of patients with HER2-positive early breast cancer (EBC), the addition of trastuzumab to chemotherapy reduced cancer recurrence and mortality by a third, compared with chemotherapy alone [3]. When administered in addition to chemotherapy, trastuzumab was also found to improve overall survival in patients with HER2-positive advanced gastric and gastroesophageal cancers [4]. Similar findings have been reported in real-world studies [5,6].

Although the advent of anti-HER2 biologics represented a breakthrough in the treatment of HER2-positive cancers, targeted biological therapies can be associated with high costs, limiting patient access in some countries [7–9]. Trastuzumab biosimilars – biological products that are highly similar to the existing, approved biologic [10] — can provide cost-effective alternatives to the reference product [11]. Several trastuzumab biosimilars have been approved or are in development [1], including CT-P6 (Herzuma®; Celltrion, Inc., Incheon, Republic of Korea [hereafter Korea]), which is associated with cost savings in comparison with reference trastuzumab [12].

CT-P6 was approved in Korea in 2014 [13] and in the United States and Europe in 2018 [14,15]. A number of clinical studies established equivalence between CT-P6 and reference trastuzumab [16]. The pivotal phase 3 clinical trial of neoadjuvant and adjuvant CT-P6 in combination with chemotherapy (CT-P6 3.2 study) demonstrated the equivalent efficacy of CT-P6 and reference trastuzumab in patients with EBC [17]. This study and an extended, phase 3/4, observational follow-up study demonstrated the long-term efficacy of CT-P6 and its comparable safety and immunogenicity profile to reference trastuzumab

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[18,19]. The effectiveness and safety of CT-P6 were also shown to be similar to reference trastuzumab in a real-world study of CT-P6 in patients with EBC or metastatic breast cancer (MBC), when administered as part of neoadjuvant or palliative dual targeted therapy in combination with chemotherapy [20]. A further real-world study in patients with EBC reported that effectiveness and safety were similar, and found that costs were reduced, with CT-P6 than with reference trastuzumab [21]. A retrospective study also found that CT-P6 had equivalent efficacy and similar safety to reference trastuzumab in patients with advanced gastric cancer [22].

Post-marketing surveillance (PMS) studies supplement evidence obtained from clinical trials, providing key evidence for drug benefit–risk assessments and pharmacovigilance data to support the introduction of new therapies into clinical practice [23,24]. The objective of this PMS study was to evaluate the safety and effectiveness of CT-P6 in a real-world setting, in patients with HER2-positive cancers. The study considered all types of adverse events (AEs), including unexpected AEs, adverse drug reactions (ADRs), and serious adverse events (SAEs).

2. Patients and methods

2.1. Study design

This open-label, observational, prospective, cohort study was conducted across 35 centers in Korea (Supplementary Table S1). Patient survey data were collected from participating investigators – via electronic case report forms – over a 1-year period (from first CT-P6 dose), from 5 October 2018 to 4 October 2022. The study was conducted in accordance with the Declaration of Helsinki, with ethical approval obtained from the local institutional review boards at each participating study site (Supplementary Table S1). All participants provided written informed consent. Data entry was periodically reviewed and monitored according to documented monitoring plans. Where necessary, queries were resolved through liaison with the relevant study site.

2.2. Patients

Enrolled patients had HER-2–positive MBC, EBC, or metastatic gastric cancer (MGC) (i.e. approved indications for CT-P6) and had not previously received CT-P6. Patients with hypersensitivity to CT-P6, CT-P6 excipients, or murine proteins were excluded from the study. Other exclusion criteria were patients who had severe dyspnea at rest, resulting from complications of advanced malignancy; patients who required supplementary oxygen therapy; and patients whom the investigator considered otherwise unfit for participation.

2.3. Treatment

CT-P6 was administered by intravenous infusion according to its approved use in Korea [25], as monotherapy or as part of combination therapy. Dosing was at either weekly (for patients with MBC or EBC) or three-weekly (for patients with MBC, EBC, or MGC) intervals. In the case of weekly infusions, these comprised a 90-minute loading dose infusion of 4 mg/kg, followed by weekly 30-minute infusions at 2 mg/kg during the maintenance phase. Patients following a three-weekly treatment schedule received a 90-minute loading dose infusion of 8 mg/kg, followed by 30-minute infusions of 6 mg/kg every 3 weeks.

2.4. Endpoints and assessments

2.4.1. Safety

Safety endpoints included AEs, evaluated according to the Medical Dictionary for Regulatory Activities (MedDRA; version 25.0), and abnormal changes to clinical test results. Echocardiograms were analyzed for clinically significant abnormal changes to cardiac function; changes to left ventricular ejection fraction (LVEF) were summarized. Safety findings were defined as 'unexpected' if they were not included in the prescribing information [25].

Assessment of AEs included assessment of SAEs and AEs leading to CT-P6 discontinuation. AE intensity was graded according to the Common Terminology Criteria for Adverse Events, version 5.0. AEs were classified as ADRs (defined as causally related to CT-P6) if the investigator deemed the relationship to CT-P6 to be 'certain,' 'probable/likely,' 'possible,' 'conditional/unclassified,' or 'unassessable/unclassifiable.' Cardiotoxicity, infusion-related reactions (IRRs), hematotoxicity (e.g. neutropenia), pulmonary diseases, oligohydramnios, and infections were classed as AEs of special interest.

2.4.2. Effectiveness

For patients with HER2-positive MBC or MGC, effectiveness was measured via objective response rate during the treatment period, using Response Evaluation Criteria in Solid Tumors, version 1.1. In trastuzumab-naïve patients, CT-P6 was considered to be 'effective' if a best overall response (BOR) of complete response or partial response was achieved. In patients who switched from trastuzumab, CT-P6 was deemed 'effective' if BOR either remained the same or improved following switch to CT-P6. For patients with HER2-positive EBC, effectiveness was evaluated in two ways: by disease progression rate before or after surgery until the end of CT-P6 administration; and by pathological complete response (pCR) rate during surgery in patients who received CT-P6 as neoadjuvant therapy. In terms of disease progression, CT-P6 was considered 'effective' if patients did not report disease progression before or after surgery until the end of CT-P6 administration. In terms of pCR, in patients who received CT-P6 as a neoadjuvant therapy, CT-P6 was considered 'effective' if pCR was achieved.

2.5. Statistical analyses

The safety population comprised all patients who received ≥ 1 dose of CT-P6 and ≥ 1 safety follow-up, either in-person or via a telephone call, after receiving CT-P6. The effectiveness population consisted of all patients in the safety population who had also completed ≥ 1 effectiveness evaluation after receiving CT-P6.

Quantitative variables were summarized using descriptive statistics, and qualitative variables were summarized by frequency and percentage of patients. Ninety-five percent confidence intervals (CIs) were calculated for incidences of safety events. In the case of factor-specific analyses, two-sided tests

were conducted at a significance level of 5%. A chi-square test with 95% CIs (Wald method) was used as the default approach. If expected frequencies of < 5 accounted for > 20% of the total data, Fisher's exact test with 95% exact CIs (Clopper–Pearson method) was used.

Factor-specific analyses of safety and effectiveness data were conducted according to demographic factors (including sex, age, and comorbidities); concomitant anticancer therapy (chemotherapy, hormone therapy, radiotherapy, and surgical intervention); and medication history. Disease stage at outset of CT-P6 treatment was also included in the effectiveness factor-specific analyses. Statistical analyses were performed using SAS software, version 9.04 (SAS Institute Inc., Cary, North Carolina).

3. Results

3.1. Patient disposition

Overall, responses were received from 35 study centers (Supplementary Table S1), for a total of 683 patients (Figure 1). Of these, 642 patients were included in the safety population and 558 in the effectiveness population.

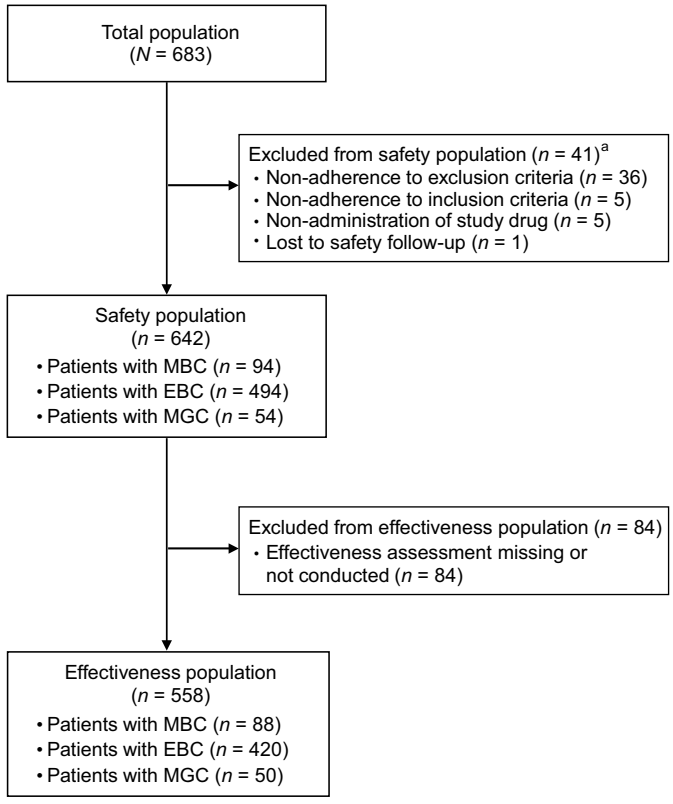

Figure 1. Patient disposition.

[a]Some patients were excluded from the safety population for multiple reasons.

Abbreviations: EBC: early breast cancer, MBC: metastatic breast cancer, MGC: metastatic gastric cancer.

3.2. Demographics and baseline characteristics

The demographics and baseline characteristics of the safety population are summarized in Table 1. The majority of patients (494/642, 76.95%) had EBC. Of the remaining patients, 94 (14.64%) had MBC and 54 (8.41%) had MGC. Most patients (596/642, 92.8%) were female. The median patient age was 55.0 (range, 29.0–89.0) years and median disease duration was 4.4 (range, 0.0–192.0) months. A minority of patients (114/642, 17.8%) had previously received trastuzumab products other than CT-P6 ('switched' patients).

3.3. Exposure to CT-P6 and other treatment

Patients received a median (range) of 17 (1–43) administrations of CT-P6 over the 1-year observation period: 15 (1–43), 17 (1–26), and 7.5 (1–19) administrations for those with MBC, EBC, and MGC, respectively. The mean (standard deviation [SD]) dose per single administration was 366 (64.9) mg: 356 (66.5), 370 (63.5), and 342 (68.9) mg for patients with MBC, EBC, and MGC, respectively.

Most patients (91/94, 96.8%) with MBC received treatment other than CT-P6. Specifically, anticancer chemotherapy was received by 83/94 (88.3%) patients, with the majority (80/94,

Table 1. Summary of patient demographics and baseline characteristics by indication (safety population).

Characteristic	Total (N = 642)	MBC (n = 94)	EBC (n = 494)	MGC (n = 54)
Sex, n (%)				
Female	596 (92.8)	94 (100.0)	493 (99.8)	9 (16.7)
Male	46 (7.2)	0	1 (0.2)	45 (83.3)
Age (years), median (range)	55 (29.0–89.0)	57 (34.0–82.0)	53 (29.0–81.0)	67 (40.0–89.0)
Height (cm), mean (SD)	157.4 (6.3)	156.0 (5.0)	156.7 (5.7)	165.5 (7.8)
Weight (kg), mean (SD)[a]	60.0 (9.8)	58.1 (10.2)	60.7 (9.7)	57.3 (8.8)
Disease duration (months), median (range)	4.4 (0.0–192.0)	1.0 (0.0–142.7)	4.7 (0.0–72.0)	1.0 (0.0–192.0)
Prior trastuzumab treatment other than CT-P6, n (%)				
No – trastuzumab naïve	528 (82.2)	79 (84.0)	396 (80.2)	53 (98.1)
Yes – switched to CT-P6	114 (17.8)	15 (16.0)	98 (19.8)	1 (1.9)
Disease stage at the start of CT-P6 administration, n (%)				
0	6 (0.9)	0	6 (1.2)	0
IA	130 (20.2)	0	130 (26.3)	0
IB	15 (2.3)	0	15 (3.0)	0
IIA	146 (22.7)	0	146 (29.6)	0
IIB	97 (15.1)	0	97 (19.6)	0
IIIA	73 (11.4)	0	73 (14.8)	0
IIIB	13 (2.0)	0	13 (2.6)	0
IIIC	14 (2.2)	0	14 (2.8)	0
IV	148 (23.1)	94 (100)	0	54 (100)

[a]Body weight measured on the first date of administration or last value before the first drug administration.

Abbreviations: EBC: early breast cancer, MBC: metastatic breast cancer, MGC: metastatic gastric cancer, SD: standard deviation.

85.1%) receiving pertuzumab. Fewer patients (12/94, 12.8%) received radiotherapy, 9/94 (9.6%) hormone therapy, and 3/94 (3.2%) surgical intervention. Treatments other than CT-P6 were received by 405/494 (82.0%) patients with EBC; the most frequently received were hormone therapy (220/494, 44.5%), as well as radiotherapy (195/494, 39.5%), anticancer chemotherapy (182/494, 36.8%), and surgical intervention (112/494, 22.7%). In line with the CT-P6 label [25], all patients (54/54, 100%) with MGC received anticancer chemotherapy with cisplatin and capecitabine (51/54, 94.4%) or fluorouracil (3/54, 5.6%).

3.4. Safety

A total of 1316 AEs were reported, across 325 (50.6%) patients (Supplementary Table S2). The most frequently reported AEs were diarrhea (61/642, 9.5%), alanine aminotransferase (ALT) increased (33/642, 5.1%), nausea (32/642, 5.0%), anemia (32/642, 5.0%), neutrophil count decreased (31/642, 4.8%), dyspepsia (27/642, 4.2%), and pruritus (27/642, 4.2%) (Supplementary Table S3). Most AEs were mild (973/1316, 73.9%) or moderate (244/1316, 18.5%) in intensity. Of the remaining AEs, 72/1316 (5.5%) were severe, 25/1316 (1.9%) were life threatening, and 2/1316 (0.2%) resulted in death (one in a patient with MBC as a consequence of neutropenic sepsis, and one in a patient with MGC due to subarachnoid hemorrhage). Overall, 21/642 patients (3.3%; comprising 4 patients with MBC, 16 with EBC, and 1 with MGC) had abnormal echocardiogram changes after CT-P6 administration; the mean (SD) LVEF across affected patients was 45.5% (10.33).

A causal relationship with CT-P6 could not be excluded for 550 cases of AEs, defined as ADRs, which were reported in 199/642 (31.0%) patients. Diarrhea was the most frequently reported ADR, followed by pruritus, neutrophil count decreased, and nausea (Table 2; Supplementary Table S4).

In 14/1316 (1.1%), 56/1316 (4.3%), and 21/1316 (1.6%) AE cases, respectively, a drug dose reduction, drug interruption/dose delay, or drug discontinuation occurred. Discontinuation of CT-P6 owing to AEs was most frequently reported with respect to cardiac failure (in 3 [0.5%] patients) and ejection fraction decreased (in 2 [0.3%] patients).

There were 348 cases of unexpected AEs in 178 (27.7%) patients. Of these, 94 unexpected ADRs were reported for 62 (9.7%) patients (Supplementary Table S2). The most common unexpected ADRs were ALT increased (12 cases in 12 [1.9%] patients), aspartate aminotransferase (AST) increased (6 cases in 6 [0.9%] patients), gastritis (7 cases in 4 [0.6%] patients), and hypokalemia (5 cases in 4 [0.6%] patients).

A total of 88 SAEs were reported for 58 (9.0%) patients and there were 28 cases of serious ADRs in 20 (3.1%) patients. The most common serious ADRs were febrile neutropenia, followed by neutrophil count decreased, asthenia, and cardiomyopathy (Table 2). Twenty-six unexpected SAEs were reported in 24 (3.7%) patients. Among these, five cases in 4 (0.6%) patients were classed as unexpected serious ADRs (Supplementary Table S2). These were intestinal obstruction, gastroenteritis, colon cancer, acute cholecystitis, and acute kidney injury.

Overall, 314 AEs of special interest occurred in 174 (27.1%) patients. These included 86 (13.4%) patients with hematotoxicity (e.g. neutropenia), 67 (10.4%) with infection, 45 (7.0%) with cardiotoxicity, 33 (5.1%) with IRRs, and 6 (0.9%) with pulmonary diseases. No cases of oligohydramnios were reported. With respect to ADRs of special interest, 129 cases were reported in 81 (12.6%) patients. These included 55 cases of hematotoxicity (e.g. neutropenia) in 36 (5.6%) patients, 28 cases of cardiotoxicity in 28 (4.4%) patients, 32 cases of IRRs in 24 (3.7%) patients, 16 cases of infection in 12 (1.9%) patients, and two cases of pulmonary diseases in 2 (0.3%) patients (Table 3).

In the overall safety population, factors associated with significant differences in ADR rate included age ($p = 0.0117$), age < 65 years versus ≥ 65 years, $p = 0.0323$), comorbidity ($p<0.0001$), presence of complications ($p < 0.0001$), cardiovascular disease ($p = 0.0018$), and previous chemotherapy ($p = 0.0002$) (Supplementary Table S5). In patients with MBC, comorbidity was associated with a difference in ADR rate. In patients with EBC, comorbidity, presence of complications, and cardiovascular disease were associated with differences in ADR rate.

3.5. Effectiveness

A total of 558 patients were included in the effectiveness analyses, following the exclusion of 84 patients in whom effectiveness assessments were missing or not conducted.

In the 88 patients with MBC included in effectiveness analyses, 74 were trastuzumab-naïve and 14 had switched to CT-P6 from other trastuzumab products. CT-P6 was rated as 'effective' in

Table 2. Summary of the four most common ADRs and serious ADRs by preferred term, per indication (safety population).

	Total ($N = 642$)	MBC ($n = 94$)	EBC ($n = 494$)	MGC ($n = 54$)
	Patients, n (%)			
ADRs				
Diarrhea	33 (5.1)	15 (16.0)	17 (3.4)	1 (1.9)
Pruritis	20 (3.1)	7 (7.4)	12 (2.4)	1 (1.9)
Neutrophil count decreased	17 (2.6)	12 (12.8)	3 (0.6)	2 (3.7)
Nausea	17 (2.6)	3 (3.2)	11 (2.2)	3 (5.6)
Serious ADRs				
Febrile neutropenia	8 (1.2)	6 (6.4)	2 (0.4)	0
Neutrophil count decreased	3 (0.5)	1 (1.1)	2 (0.4)	0
Asthenia	2 (0.3)	0	2 (0.4)	0
Cardiomyopathy	2 (0.3)	1 (1.1)	1 (0.2)	0

Abbreviations: ADR: adverse drug reaction, EBC: early breast cancer, MBC: metastatic breast cancer, MGC: metastatic gastric cancer.

Table 3. Summary of AEs and ADRs of special interest, per indication (safety population).

	Total ($N = 642$)	MBC ($n = 94$)	EBC ($n = 494$)	MGC ($n = 54$)
	Patients, n (%)			
AEs of special interest	174 (27.1)	55 (58.5)	101 (20.4)	18 (33.3)
Cardiotoxicity	45 (7.0)	13 (13.8)	30 (6.1)	2 (3.7)
IRR	33 (5.1)	13 (13.8)	16 (3.2)	4 (7.4)
Hematotoxicity (e.g. neutropenia)	86 (13.4)	38 (40.4)	35 (7.1)	13 (24.1)
Pulmonary diseases	6 (0.9)	2 (2.1)	4 (0.8)	0
Oligohydramnios	0 (0.0)	0	0	0
Infection	67 (10.4)	15 (16.0)	49 (9.9)	3 (5.6)
ADRs of special interest	81 (12.6)	32 (34.0)	43 (8.7)	6 (11.1)
Cardiotoxicity	28 (4.4)	9 (9.6)	18 (3.6)	1 (1.9)
IRR	24 (3.7)	11 (11.7)	11 (2.2)	2 (3.7)
Hematotoxicity (e.g. neutropenia)	36 (5.6)	19 (20.2)	14 (2.8)	3 (5.6)
Pulmonary diseases	2 (0.3)	0	2 (0.4)	0
Oligohydramnios	0	0	0	0
Infection	12 (1.9)	3 (3.2)	9 (1.8)	0

Abbreviations: ADR: adverse drug reaction, AE: adverse event, EBC: early breast cancer, IRR: infusion-related reaction, MBC: metastatic breast cancer, MGC: metastatic gastric cancer.

40.5% (30/74) of trastuzumab-naïve patients and in 28.6% (4/14) of switched patients (Table 4). BOR for trastuzumab-naïve patients with MBC included 6/74 (8.1%) patients with complete response (CR), 24/74 (32.4%) patients with partial response (PR), and 28/74 (37.8%) patients with stable disease. Progressive (PD) or relapsed disease (RD) was observed in 15/74 (20.3%) patients, and 1/74 patient (1.4%) was not evaluated (i.e. no tumor evaluation occurred before the administration of CT-P6).

Of the 420 patients with EBC included in effectiveness analyses, disease progression was evaluated before surgery in 113 patients (of whom 104 were treatment-naïve and 9 were switched) and after surgery in 367 patients (of whom 289 were treatment-naïve and 78 were switched). The vast majority of trastuzumab-naïve EBC patients did not report disease progression before (101/104, 97.1%) or after (280/289, 96.9%) surgery. In switched EBC patients, no patients (0/9) reported disease progression prior to surgery and the majority of patients (75/78, 96.2%) experienced no disease progression after surgery. Among the 106 trastuzumab-naïve patients with EBC who received CT-P6 as neoadjuvant therapy and for whom effectiveness information was available, pCR occurred in 34/106 (32.1%) patients after receiving neoadjuvant CT-P6; 70.0% (7/10) of switched patients achieved pCR (Table 4).

Fifty patients with MGC were included in efficacy analyses, of whom 49 were trastuzumab-naïve and one was switched. CT-P6 was rated as 'effective' in 24/49 (49.0%) trastuzumab-naïve patients with MGC (Table 4). CR occurred in 2/49 (4.1%) patients, 22/49 (44.9%) patients reported PR, and stable disease was

Table 4. Summary of effectiveness, by indication (effectiveness population).

	Effective	Ineffective
	Patients, n/N (%)	
MBC		
Trastuzumab naïve[a]	30/74 (40.5)	44/74 (59.5)[b]
Switched[c]	4/14 (28.6)	10/14 (71.4)[b]
MGC		
Trastuzumab naïve[a]	24/49 (49.0)	25/49 (51.0)
Switched[c]	1/1 (100.0)	0/1
EBC		
No disease progression before surgery[d]		
Trastuzumab naïve	101/104 (97.1)	3/104 (2.9)
Switched	9/9 (100.0)	0/9
No disease progression after surgery[d]		
Trastuzumab naïve	280/289 (96.9)	9/289 (3.1)
Switched	75/78 (96.2)	3/78 (3.9)
Pathological complete response[e]		
Trastuzumab naïve[f]	34/106 (32.1)	64/106 (60.4)
Switched	7/10 (70.0)	3/10 (30.0)

[a]In trastuzumab-naïve patients, CT-P6 was considered to be 'effective' if a BOR of complete or partial response was achieved.
[b]CT-P6 was considered to be 'ineffective' for 1 and 7 patients who had missing baseline effectiveness results in the MBC trastuzumab-naïve and MBC switched groups, respectively.
[c]In switched patients, CT-P6 was considered to be 'effective' if BOR either remained the same or improved following switch to CT-P6.
[d]CT-P6 was considered to be 'effective' if patients with EBC did not report disease progression before or after surgery until the end of CT-P6 administration.
[e]CT-P6 was considered to be 'effective' in patients with EBC who received CT-P6 as neoadjuvant therapy if they achieved pathological complete response.
[f]Among 106 patients, 8 (7.5%) did not receive surgery; therefore, CT-P6 was not considered to be 'effective' or 'ineffective.'
Abbreviations: BOR: best overall response, EBC: early breast cancer, MBC: metastatic breast cancer, MGC: metastatic gastric cancer.

achieved in 10/49 (20.4%) patients. PD/RD was reported in 15/49 (30.6%) patients. The single 'switched' patient in this group achieved a PR and CT-P6 was considered 'effective.'

In factor-specific analyses, no significant differences were observed in effectiveness rates for patients with MBC or MGC. In 116 patients with EBC who received CT-P6 as neoadjuvant therapy, medical history was associated with significant differences in pCR rate (p=0.0292), with 15 (24.6%) and 26 (47.3%) patients with and without medical history, respectively, achieving pCR.

4. Discussion

This PMS study included patients with MBC, EBC, and MGC who received treatment with CT-P6 during routine clinical practice in Korea. Overall, the safety findings from this study were aligned with the established safety profiles of reference trastuzumab and CT-P6 with regards to AEs, ADRs, SAEs, serious ADRs, and AEs/ADRs of special interest. Effectiveness findings were also consistent with those from previous studies of CT-P6 [17–21].

Diarrhea, pruritus, neutrophil count decreased, and nausea were the most common ADRs identified in this study. Diarrhea, neutropenia, and nausea have been reported as AEs/ADRs in previous real-world studies evaluating CT-P6 [21,22]. These events were also among the most common treatment-emergent adverse events (TEAEs) and study drug–related TEAEs during the overall CT-P6 3.2 study period [18]. In addition, based on clinical trial and PMS studies, the trastuzumab European prescribing information lists the incidence of diarrhea, neutropenia, and nausea as very common (≥1/10) and that of pruritus as common (≥1/100 to < 1/10) [15], as does the Korean prescribing information [25].

Events observed in this study that were not mentioned in the Korean prescribing information for CT-P6 [25] were classified as 'unexpected' events. These comprised 348 unexpected AEs (affecting 27.7% of patients) and 94 unexpected ADRs (affecting 9.7% of patients). The most frequent unexpected ADR was ALT increased, followed by AST increased; however, both the Korean and European prescribing information describe hepatocellular injury as a 'common' adverse reaction with trastuzumab treatment [15,25], which encompasses elevations in ALT and AST [26].

In this PMS study, the AE/ADR of special interest of cardiotoxicity was captured using the standardized MedDRA query of cardiac failure; AEs and ADRs of cardiotoxicity were reported in 7.0% and 4.4% of patients, respectively. This is aligned with the 'common' incidence of cardiac failure (congestive) in the European prescribing information [15]. Given differences in assessment criteria, direct comparisons with previous studies are not appropriate; however, findings appear generally similar to the 10.0% incidence of AEs of heart failure reported in a retrospective study in patients with advanced gastric cancer [22], and the rates of heart failure (TEAEs: 1.8%) and cardiac disorders (TEAEs: 8.5%; treatment-related TEAEs: 6.3%) reported during the neoadjuvant period of the CT-P6 3.2 study [17]. In addition, the mean (SD) LVEF after CT-P6 treatment (45.5% [10.33]) in the current study was broadly comparable with findings from previous studies evaluating CT-P6 in patients with EBC (mean [95% CI]: 65.9% [65.0, 66.8] [20]; median [range]: 61.5 [47, 75] [21] and 64.0 [44.0, 82.0] [17]).

In terms of other AEs/ADRs of special interest, the incidence of IRRs (AEs: 5.1%; ADRs: 3.7%) was slightly lower than the 'very common' incidence in the European prescribing information [15], but was broadly aligned with findings from a retrospective study in patients with EBC (AEs: 5.0%) [21] as well as the neoadjuvant period of the CT-P6 3.2 study (TEAEs: 8.5%; treatment-related TEAEs: 5.2%) [17]. AEs of hematotoxicity (e.g. neutropenia) were reported in 13.4% patients in the current study; while the European prescribing information does not provide overall incidence rates for hematotoxicity events, neutropenia and thrombocytopenia are both described as 'very common' events [15]. In addition, hematologic toxicities accounted for the most frequent AEs in a retrospective study in patients with advanced gastric cancer [22], and the System Organ Class 'blood and lymphatic system disorders' had the second highest incidence of reported TEAEs during the CT-P6 3.2 study [18]. Finally, the incidence of infections (AEs: 10.4%; ADRs: 1.9%) was generally similar to that of the CT-P6 3.2 study neoadjuvant period (TEAEs: 20.3%; treatment-related TEAEs: 4.4%) [17] and broadly aligned with the 'very common' incidence described in the European prescribing information [15]. There was a low incidence of pulmonary diseases in the current study (0.9% of patients), contrasting with the 'common' incidence of lung disorders reported in the European prescribing information [15], while the absence of oligohydramnios in the current study may be expected, given that the frequency could not be estimated in the European prescribing information on the basis of available data [15].

There was a low incidence of drug dose reductions or interruptions owing to AEs, in keeping with the absence of dosing changes owing to AEs among 20 patients receiving neoadjuvant treatment for EBC in a retrospective study [21]. In the current study,19 (3.0%) and 10 (1.6%) patients discontinued study drug owing to AEs and ADRs, respectively. These rates are broadly comparable to findings from previous studies, with 1 (1.7%) patient with HER2-positive breast cancer discontinuing CT-P6 owing to serious ADRs in a prospective, hospital-based, intensive safety monitoring study [27] and 7/271 (2.6%) patients in the CT-P6 group discontinuing the CT-P6 3.2 study owing to TEAEs [17]. Cardiac failure was the only AE/ADR leading to discontinuation of CT-P6 in more than one patient, affecting 3 (0.5%) patients in both cases. This relationship was also reported in a retrospective study in patients with advanced gastric cancer, where one of three patients with heart failure (of 30 CT-P6–treated patients overall) discontinued CT-P6 [22]. In the current study, ejection fraction decreased was the only other AE leading to CT-P6 discontinuation in more than one patient (reported in 2 [0.3%] patients). Previously, CT-P6 treatment interruption was reported in one of three patients with a LVEF reduction to < 50% in a retrospective study of 38 CT-P6–treated patients with MBC [20]. Implementing treatment changes in response to heart failure and LVEF decreases aligns with recommendations in the European prescribing information to suspend treatment if LVEF decreases ≥ 10 points from baseline and below 50%, and to strongly consider discontinuing trastuzumab if LVEF does not improve or symptomatic congestive heart failure occurs [15].

Safety factor-specific analyses were also conducted to identify factors associated with differences in ADR incidences. These were primarily known risk factors included in the European prescribing information for CT-P6 [15], including medical history of heart disease as a risk factor for cardiac dysfunction, and medical history of heart disease, age >50 years, and prior chemotherapy as risk factors for cardiac dysfunction, hematotoxicity, and pulmonary AEs.

In terms of effectiveness findings, only a small number of patients with EBC experienced disease progression before or after surgery, consistent with other clinical trial data for neoadjuvant CT-P6 [28]. Rates of CR/PR were broadly aligned with previous real-world studies of CT-P6 in patients with MBC (CR 5.3%; PR 73.7% [20]) and MGC (CR 0%; PR 56.7% [22]). However, the pCR rate in trastuzumab-naïve patients with EBC (32.1%) was lower than in previous real-world studies (74.4% [20] and 65.0% [21]) and clinical trials (46.8% [17] and 43.3%/45.2% [<65 years/ ≥65 years] [28]) evaluating neoadjuvant CT-P6, contrasting with the 70.0% pCR rate identified in the 10 switched patients. Nevertheless, the results of this study are in line with trastuzumab data: in combination with standard chemotherapy, neoadjuvant trastuzumab has been reported to induce pCR rates of around 30% in patients with HER2-positive breast tumors [29]. Factor-specific analyses did not identify factors significantly associated with effectiveness in patients with MBC or MGC, but in patients with EBC, past medical history was significantly associated with the likelihood of achieving pCR. The small number of patients evaluated for pCR in the current study limits the interpretation of comparisons to other studies.

This prospective PMS study evaluated the safety and effectiveness of CT-P6 in routine clinical practice, in a substantial overall patient population. Notably, patients were followed up for a maximum of 1 year; however, given that longer treatment periods have been described in other real-world studies [30], future PMS of CT-P6 could benefit from a longer observation period. Additionally, while the study was conducted in a large number of centers across Korea, this was a single-country study. As such, the findings are likely to be representative of the wider patient population in the region but, given that treatment practices can differ between countries, may not be generalizable globally. A further limitation of the study is the relatively small populations of patients with MBC ($n = 94$) and MGC ($n = 54$), compared with EBC ($n = 494$), limiting the detection of any specific safety findings and the analysis of effectiveness in these indications. In the future, further pharmacovigilance reporting will be undertaken, to provide further information on the safety of CT-P6 in routine clinical practice. Finally, factor-specific analyses suggested that medical history was associated with significant differences in pCR rate; however, risk factor analysis was not performed as limited information was collected from patients. Therefore, future studies could perform risk factor analysis to increase understanding of risk factors associated with CT-P6 treatment outcomes.

5. Conclusions

This PMS study conducted in routine clinical practice in Korea did not identify any safety or effectiveness findings that impact the established benefit–risk profile of CT-P6 for the treatment of patients with MBC, EBC, or MGC.

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Declaration of interest

MH Park, JH Seo, JH Park, M-K Seong, KU Park, MK Kim, M Chang, S-J Koh, MH Lee, ST Lim, YB Yoo, SY Oh, and TH Kim have nothing to disclose. SH Kim is an employee of Celltrion, Inc., has a leadership role in Celltrion, Inc., and has stocks for Celltrion, Inc. KY Ahn, TH Park, H Ju, S Kim, N Kim, and E Lee are employees of Celltrion, Inc. and have stocks for Celltrion, Inc. EH Baek is an employee of Celltrion, Inc. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Ethics statement

The study was conducted in accordance with the Declaration of Helsinki, with ethical approval obtained from the local institutional review boards at each participating study site (**Supplementary Table S1**). All participants provided written informed consent.

Author contributions

MH Park, JH Seo, JH Park, M-K Seong, KU Park, MK Kim, M Chang, S-J Koh, MH Lee, ST Lim, YB Yoo, SY Oh, and TH Kim contributed to the data collection and the interpretation of study data. SH Kim, KY Ahn, TH Park, H Ju, and EH Baek contributed to the design of the study and the analysis or interpretation of study data. S Kim, N Kim, and E Lee contributed to the analysis or interpretation of study data. All authors reviewed and critically revised the manuscript, approved the final draft, and are accountable for the accuracy and integrity of the research.

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Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

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