BioDrugs (2023) 37:433–440
https://doi.org/10.1007/s40259-023-00582-w

SHORT COMMUNICATION

Six-Year Survival Outcomes for Patients with HER2-Positive Early Breast Cancer Treated with CT-P6 or Reference Trastuzumab: Observational Follow-Up Study of a Phase 3 Randomised Controlled Trial

Justin Stebbing[1,2,3] · Yauheni Baranau[4] · Valery Baryash[4] · Vladimir Moiseyenko[5] · Dmytro Boliukh[6] · Nicoleta Antone[7] · Alexey Manikhas[8] · Anatolii Chornobai[9] · Taehong Park[10] · Eric Hyungseok Baek[10] · Jaeyong Lee[11] · Jiin Choi[11] · Nahyun Kim[11] · Keumyoung Ahn[10] · Sang Joon Lee[12] · Sunghyun Kim[13]

Accepted: 19 January 2023 / Published online: 7 March 2023

Abstract

Background The Phase 3 CT-P6 3.2 study demonstrated equivalent efficacy and comparable safety between CT-P6 and reference trastuzumab in patients with human epidermal growth factor receptor-2 (HER2)-positive early breast cancer after up to 3 years' follow-up.

Objective To investigate long-term survival with CT-P6 and reference trastuzumab.

Methods In the CT-P6 3.2 study, patients with HER2-positive early breast cancer were randomised to neoadjuvant chemotherapy with CT-P6 or reference trastuzumab, surgery, and adjuvant CT-P6 or reference trastuzumab before a 3-year post-treatment follow-up. Patients who completed the study could enter a 3-year extension (CT-P6 4.2 study). Data were collected every 6 months to assess overall survival (OS), disease-free survival (DFS), and progression-free survival (PFS).

Results Of 549 patients enrolled in the CT-P6 3.2 study, 216 (39.3%) patients continued in the CT-P6 4.2 study (CT-P6, 107; reference trastuzumab, 109) (intention-to-treat extension set). Median follow-up was 76.4 months for both groups. Medians were not reached for time-to-event parameters; estimated hazard ratios (95% confidence intervals) for CT-P6 versus reference trastuzumab were 0.59 (0.17–2.02) for OS, 1.07 (0.50–2.32) for DFS, and 1.08 (0.50–2.34) for PFS. Corresponding 6-year survival rates in the CT-P6 and reference trastuzumab groups, respectively, were 0.96 (0.90–0.99) and 0.94 (0.87–0.97), 0.87 (0.78–0.92) and 0.89 (0.81–0.94), and 0.87 (0.78–0.92) and 0.89 (0.82–0.94).

Conclusions Data from this extended follow-up of the CT-P6 3.2 study demonstrate the comparable long-term efficacy of CT-P6 and reference trastuzumab up to 6 years.

EudraCT number 2019-003518-15 (retrospectively registered 10 March 2020).

1 Introduction

CT-P6 is a biosimilar of reference trastuzumab that is approved for the treatment of human epidermal growth factor receptor (HER2)-positive early and metastatic breast cancer by the US Food and Drug Administration and European Medicines Agency [1, 2]. Equivalence in terms of efficacy and comparable safety was demonstrated between CT-P6 and reference trastuzumab in patients with HER2-positive early breast cancer in a randomised, Phase 3 clinical trial (the CT-P6 3.2 study, NCT02162667; EudraCT number: 2013-004525-84) [3–5]. After 3 years' follow-up, disease-free survival (DFS), progression-free survival (PFS) and overall survival (OS) rates remained similar between patients treated with CT-P6 and reference trastuzumab, supporting the conclusion of equivalence in terms of efficacy over the long term [5]. Findings agreed with 3-year time-to-event rates reported for neoadjuvant and adjuvant reference trastuzumab in other studies, including HannaH [6], NeoALTTO [7] and JBCRG-10 [8]. CT-P6 was well tolerated, with a safety profile comparable to that of reference trastuzumab throughout the 3-year follow-up, including in terms of drug-related cardiac disorders and decreases in left ventricular ejection fraction [5]. Immunogenicity was also similar between groups [5]. After a median of 38.7 months

Extended author information available on the last page of the article

Key Points

The equivalent efficacy and comparable safety and immunogenicity of CT-P6 to reference trastuzumab was demonstrated in the randomised, Phase 3 CT-P6 3.2 study, which compared the products administered as neoadjuvant and post-surgery adjuvant treatment in patients with human epidermal growth factor receptor-2 (HER2)-positive early breast cancer.

The current study, CT-P6 4.2, was a further 3-year extension to the 3 years of follow-up included in the CT-P6 3.2 study, providing efficacy data after a median of 76.4 months of follow-up.

Our data extend the findings of the CT-P6 3.2 study, demonstrating the comparable long-term effects of CT-P6 and reference trastuzumab on overall survival, disease-free survival, and progression-free survival over up to 6 years.

and 39.6 months of follow-up in the CT-P6 and reference trastuzumab groups, respectively, median DFS, PFS and OS were not reached [5].

This article reports the findings of the CT-P6 4.2 study—an extended observational follow-up study of patients in the CT-P6 3.2 study—which was conducted to provide additional long-term data on the efficacy of CT-P6 relative to reference trastuzumab. We report survival outcomes after a period of up to 6 years.

2 Methods

2.1 Study Design

The CT-P6 4.2 study (EudraCT number: 2019-003518-15) was a multicentre, observational, extended follow-up study of patients who completed the last follow-up visit in the CT-P6 3.2 study. In countries where CT-P6 had already received regulatory approval, CT-P6 4.2 was conducted as a Phase 4 study. In all other countries (Belarus, Russia and Ukraine), it was considered a Phase 3 study.

Full details of the study design for the randomised, double-blind, active-controlled CT-P6 3.2 study, including randomisation procedures, have been published previously [3, 4]. In brief, patients were recruited into the CT-P6 3.2 study from 112 centres across 23 countries. Neoadjuvant treatment consisted of eight 3-week cycles of CT-P6 (Herzuma®; Celltrion, Inc., Incheon, Republic of Korea) or reference trastuzumab (Herceptin®; Genentech, San Francisco, CA, USA), consisting of a loading dose of 8 mg/kg on Day 1 of Cycle 1 followed by 6 mg/kg on Day 1 of Cycles 2–8, with docetaxel and fluorouracil, epirubicin and cyclophosphamide, followed by surgery. Post-surgery, patients received up to ten cycles of adjuvant CT-P6 or reference trastuzumab (6 mg/kg administered every 3 weeks, per original randomisation), and were followed for up to 3 years from the date of enrolment of the last patient.

Patients who completed the last follow-up visit of the CT-P6 3.2 study could participate in the CT-P6 4.2 study, and could be enrolled irrespective of their study treatment completion status (Fig. 1). No study drugs were administered during the CT-P6 4.2 study.

At the on-site enrolment visit, data regarding survival status, disease progression/recurrence and initiation of any anticancer therapies since the end of the CT-P6 3.2 study were collected directly from the patients or obtained from medical charts. For patients who died during the ~ 1-year period between the end of their participation in the CT-P6 3.2 study and the beginning of the current study, survival data, assessment dates for progressive/recurrent disease, and the start date of breast cancer-related therapy were retrospectively collected from medical charts or patients' relatives, where possible.

After enrolment in the CT-P6 4.2 study, survival status, disease progression/recurrence, and anticancer treatment initiation data were collected via telephone every 6 months (± 21 days). Data were collected from the patients, their medical charts, or from relatives in case of patient death. Patient data collection ceased with a final visit or telephone call at the end of the 3-year CT-P6 4.2 study follow-up period, upon withdrawal of the patient from the study, or with the death of the patient.

The study was conducted in accordance with the ethical principles originating in the Declaration of Helsinki, Good Clinical Practice, and all applicable laws or regulations. Before the start of the study, the protocol, informed consent form, advertisements to be used for the recruitment of study patients, and any other written information to be provided to the patients were approved by the institutional review board and/or independent ethics committee at each site (Table S1; Online Supplemental Material (OSM), Resource 1). All patients provided written informed consent before entering the study.

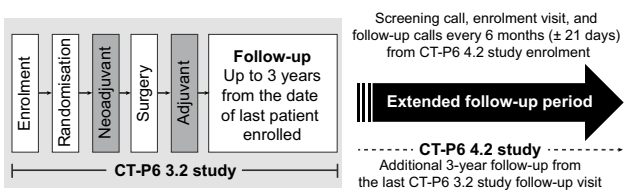

Fig. 1 Study design

2.2 Eligibility Criteria

Detailed eligibility criteria for the CT-P6 3.2 study have been published previously [3, 4]. In the CT-P6 4.2 study, eligible patients were females aged ≥ 18 years with pathologically confirmed, newly diagnosed, operable, early breast cancer (Stage I, II or IIIA) at initiation of the CT-P6 3.2 study. Patients had completed the last follow-up visit of the CT-P6 3.2 study, which took place around October 2018, regardless of their study treatment completion status. Patients who died during the CT-P6 3.2 study were excluded.

2.3 Endpoints

Follow-up duration for the efficacy endpoints of OS, DFS and PFS was defined as the interval between the date of randomisation in the CT-P6 3.2 study and the date of the last available information. OS was defined as the interval between the date of randomisation in the CT-P6 3.2 study and the date of death from any cause. DFS was defined as the interval between the date of breast surgery in the CT-P6 3.2 study and the date of disease progression/recurrence or death from any cause, whichever occurred first. Only disease progression/recurrence that occurred after breast surgery and before or at anticancer therapy initiation was regarded as an event. PFS was defined as the interval between the date of CT-P6 3.2 study randomisation and the date of disease progression/recurrence or death from any cause, whichever occurred first. Only disease progression/recurrence that occurred before or at anticancer therapy initiation was regarded as an event.

2.4 Statistical Analysis

A sample size justification based on a statistical hypothesis was not relevant in this study. Time-to-event analyses were conducted in the intention-to-treat (ITT) and ITT extension sets. The ITT set comprised all randomised patients in the CT-P6 3.2 study, regardless of whether study treatment was received. The ITT extension study set comprised all patients in the ITT set for whom data were collected during the extension study (the CT-P6 4.2 study), including patients who died or experienced disease progression/recurrence between the end of their participation in the CT-P6 3.2 study and the beginning of the CT-P6 4.2 study. Percentages for event data were calculated based on numbers of patients within the treatment group for the population of interest, unless otherwise indicated. Median survival times for time-to-event endpoints were estimated using the Kaplan–Meier method; corresponding 95% confidence intervals (CIs) are shown in the format [*x*–*y*), where a square bracket denotes that the start of the range is inclusive of x, and a parenthesis denotes that the end of the range is exclusive of *y*. Survival rates after 4, 5 and 6 years were estimated using the Kaplan–Meier method and presented alongside the corresponding 95% CIs. An adjusted, stratified Cox regression model was used to estimate hazard ratios (HRs) and corresponding 95% CIs for CT-P6 compared with reference trastuzumab. Stratification factors from the CT-P6 3.2 study were used as covariates: disease stage (Stage I/II vs. Stage IIIA and above), oestrogen receptor status (positive vs. negative), progesterone receptor status (positive vs. negative), and region (Europe, the Middle East, and Africa vs. America vs. Asia). Statistical analyses were performed using SAS (SAS Institute Inc., Cary, NC, USA), version 9.4.

3 Results

3.1 Patients

Of 549 patients enrolled in the CT-P6 3.2 study (the ITT set), 216 (39.3%) patients were included in the CT-P6 4.2 extension study. The first patient's first visit for the CT-P6 4.2 study was on 14 January 2020, with the final follow-up visit conducted on 21 October 2021. In total, 107 (39.5%) patients in the CT-P6 group from the CT-P6 3.2 study and 109 (39.2%) patients in the reference trastuzumab group had evaluable data in the CT-P6 4.2 study and made up the ITT extension set. Patient disposition information is presented in Table S2 (OSM Resource 1).

Baseline patient demographics and disease characteristics were balanced overall between the CT-P6 and reference trastuzumab groups in both the ITT and ITT extension sets (Table 1). Most patients had Stage IIA to Stage IIIA disease. More than half were oestrogen receptor-positive and over one-third were progesterone receptor-positive. Of note, the majority of patients (78.5%) in the ITT set were from European sites, with 17.5% from Asian sites and 4.0% from American sites, but all patients (100%) in the ITT extension set were recruited at European sites.

3.2 Survival Results

In the ITT set, the median [95% CI) follow-up duration was 42.6 [40.3–45.3) months and 42.6 [41.3–44.0) months for the CT-P6 and reference trastuzumab groups, respectively. Correspondingly, in the ITT extension set, the median follow-up duration was 76.4 [75.4–77.7) months and 76.4 [75.1–78.2) months.

Median OS was not reached in either group in the ITT or ITT extension sets owing to an insufficient number of events. Overall, in the ITT set, 22 (8.1%) and 25 (9.0%) patients died in the CT-P6 and reference trastuzumab groups, respectively; correspondingly, four (3.7%) and seven (6.4%) patients died in the ITT extension set (Table S3, OSM Resource 1).

Estimated HRs (95% CIs) for OS were 0.95 (0.53–1.68) and 0.59 (0.17–2.02) for the ITT and ITT extension sets, respectively (Fig. 2).

Median DFS was not reached in either group (in either analysis set) owing to an insufficient number of events. In the ITT set, 47 (18.2%) patients in the CT-P6 and 42 (16.1%) patients in the reference trastuzumab group died or had progressive disease (PD)/recurrence after surgery. In the ITT extension set, the respective numbers of patients who died or had PD/recurrence were 13 (12.3%) and 13 (12.1%) (Table S3, OSM Resource 1). The estimated HRs (95% CI) for DFS were 1.18 (0.77–1.80) in the ITT set and 1.07 (0.50–2.32) in the ITT extension set (Fig. 3).

Median PFS was not reached in the CT-P6 or reference trastuzumab groups in either the ITT or ITT extension sets owing to an insufficient number of events. In the ITT set, 54 (19.9%) patients in the CT-P6 group and 46 (16.5%) patients in the reference trastuzumab group died or had PD/recurrence; corresponding values in the ITT extension set were 13 (12.1%) and 13 (11.9%), respectively (Table S3, OSM Resource 1). The estimated HRs (95% CI) for PFS were 1.25 (0.84–1.87) in the ITT set and 1.08 (0.50–2.34) in the ITT extension set (Fig. 4).

Kaplan–Meier analyses were used to estimate OS, DFS and PFS rates at 4, 5 and 6 years of follow-up. Rates were comparable between treatment groups in both the ITT and ITT extension sets (Table S4, OSM Resource 1). In the ITT set, the estimated 6-year OS rate (95% CI) was 0.89 (0.84–0.93) in the CT-P6 group and 0.87 (0.81–0.91) in the reference trastuzumab group. Correspondingly, 6-year DFS rates (95% CI) were 0.78 (0.71–0.83) and 0.81 (0.75–0.86), and 6-year PFS rates (95% CI) were 0.76 (0.69–0.81) and 0.80 (0.73–0.85). Estimated 6-year time-to-event rates in the ITT extension set were comparable. For the CT-P6 and

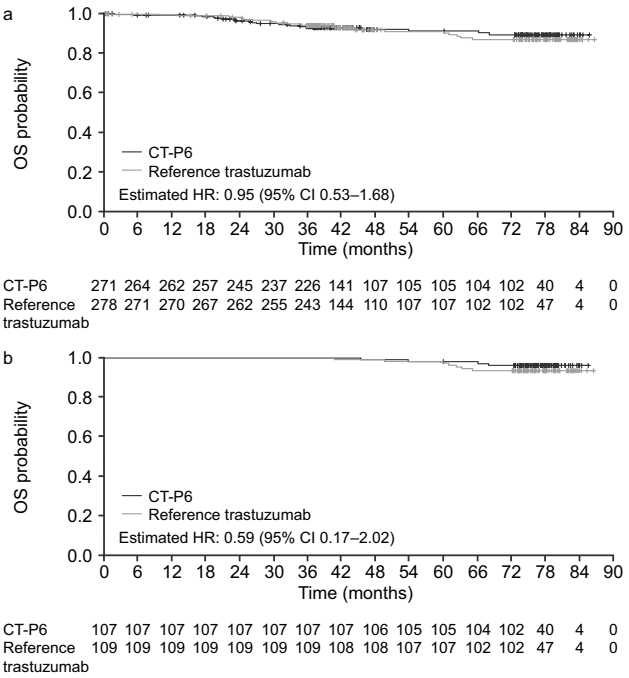

Fig. 2 Kaplan–Meier plot of OS. (**a**) ITT set; (**b**) ITT extension set. *CI* confidence interval, *HR* hazard ratio, *ITT* intention-to-treat, *OS* overall survival

Table 1 Patient demographics and baseline disease characteristics

Characteristic	ITT set ($n = 549$)		ITT extension set ($n = 216$)	
	CT-P6 ($n = 271$)	Reference trastuzumab ($n = 278$)	CT-P6 ($n = 107$)	Reference trastuzumab ($n = 109$)
Age, median (range), years	53.0 (24–78)	53.0 (22–74)	54.0 (30–73)	51.0 (26–71)
Disease stage, *n* (%)				
I	23 (8.5)	31 (11.2)	10 (9.3)	12 (11.0)
IIA	75 (27.7)	86 (30.9)	31 (29.0)	33 (30.3)
IIB	105 (38.7)	98 (35.3)	46 (43.0)	46 (42.2)
IIIA	64 (23.6)	61 (21.9)	18 (16.8)	18 (16.5)
IIIB	1 (0.4)	0	0	0
IIIC	3 (1.1)	1 (0.4)	2 (1.9)	0
IV	0	1 (0.4)	0	0
HER2-positive, *n* (%)	271 (100.0)	278 (100.0)	107 (100.0)	109 (100.0)
Hormone receptor-positive, *n* (%)[a]	160 (59.0)	162 (58.3)	61 (57.0)	66 (60.6)
Oestrogen receptor-positive	154 (56.8)	154 (55.4)	60 (56.1)	62 (56.9)
Progesterone receptor-positive	112 (41.3)	108 (38.8)	40 (37.4)	47 (43.1)

ITT intention-to-treat

[a]Positive for oestrogen receptor or progesterone receptor

reference trastuzumab groups, respectively, rates (95% CI) were 0.96 (0.90–0.99) and 0.94 (0.87–0.97) for OS, 0.87 (0.78–0.92) and 0.89 (0.81–0.94) for DFS, and 0.87 (0.78–0.92) and 0.89 (0.82–0.94) for PFS.

4 Discussion

Approximately 40% of the patients with HER2-positive early breast cancer who enrolled in the CT-P6 3.2 study entered the CT-P6 4.2 extension study. After a median follow-up duration of 76.4 months in each group, OS, DFS and PFS rates were comparable between CT-P6 and reference trastuzumab, providing further support of the biosimilarity of CT-P6 to reference trastuzumab demonstrated in the CT-P6 3.2 study [3–5].

Our findings are comparable with long-term data from other Phase 3 studies that have evaluated the treatment of HER2-positive early breast cancer with reference trastuzumab or its biosimilars. In the current study, we report 6-year OS rates for CT-P6 and reference trastuzumab of 89% and 87%, respectively, in the ITT set (96% and 94% in the ITT extension set, respectively). The HannaH trial reported a 6-year OS rate for reference trastuzumab of 84% for patients receiving neoadjuvant and adjuvant therapy including intravenous reference trastuzumab [9], and the NeoALTTO trial (BIG 1-06) reported a 6-year OS rate of

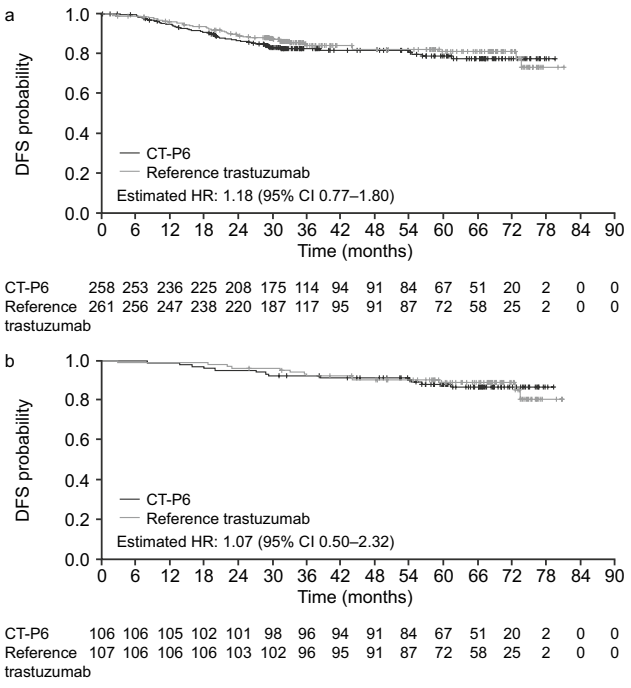

Fig. 3 Kaplan–Meier plot of DFS. (**a**) ITT set; (**b**) ITT extension set. *CI* confidence interval, *DFS* disease-free survival, *HR* hazard ratio, *ITT* intention-to-treat

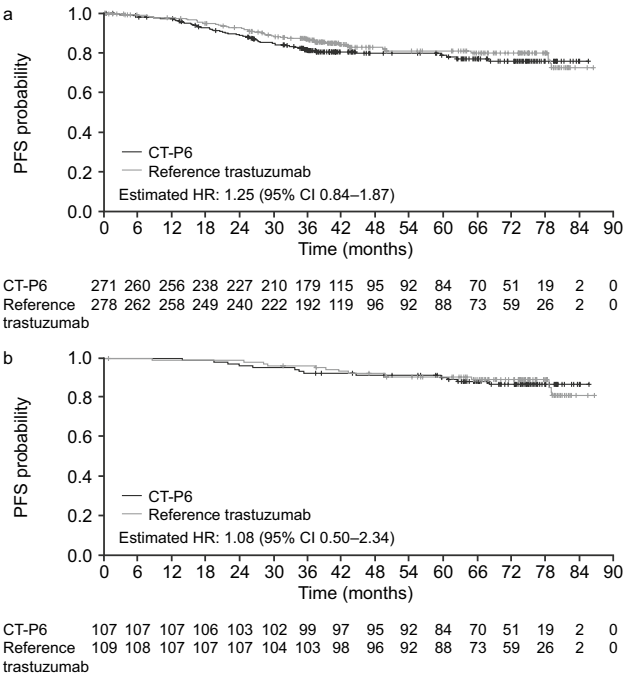

Fig. 4 Kaplan–Meier plot of PFS. (**a**) ITT set; (**b**) ITT extension set. *CI* confidence interval, *HR* hazard ratio, *ITT* intention-to-treat, *PFS* progression-free survival

79% with neoadjuvant and adjuvant reference trastuzumab [10]. In the APHINITY (BIG4-11) trial, 6-year OS with adjuvant reference trastuzumab was 94% [11], while 5-year OS was 94% in the SafeHER trial [12]. In addition, a long-term follow-up of a Phase 3 study of SB3 (a biosimilar of reference trastuzumab) in the neoadjuvant setting for HER2-positive early or locally advanced breast cancer reported a 5-year OS rate of 93% for SB3 and 87% for reference trastuzumab [13]. Outside of the clinical trial setting, OS rates for reference trastuzumab are similar: a large, population-based cohort derived from the Netherlands Cancer Registry reported 5-year OS rates of 90% in HER2-positive early breast cancer [14], while an extended follow-up of an observational cohort study in Japan (JBCRG-01) reported a 5-year OS rate of 96% [15].

With regards to DFS, the 6-year rates we report for CT-P6 and reference trastuzumab in this study (78% and 81% in the ITT set, and 87% and 89% in the ITT extension set, respectively) are in keeping with 5-year rates from the Phase 3 SafeHER trial (87%) [12] and the Phase 2 NeoSphere trial (81%) [16], as well as with observational data from the JBCRG-01 cohort study (89%) [15].

To our knowledge, there are no PFS data for reference trastuzumab in this patient population over a similar time frame, although some comparison may be drawn with 6-year event-free survival rates from the HannaH (65%) [9] and NeoALTTO trials (67%) [10]. Here we report 6-year PFS

rates of 76% and 80% in the ITT set and 87% and 89% in the ITT extension set for CT-P6 and reference trastuzumab, respectively.

Real-world retrospective data from Korea suggest that clinical outcomes with CT-P6 and reference trastuzumab are comparable [17]. A similar percentage of patients with HER2-positive early breast cancer achieved a pathologic complete response with CT-P6 (74.4% [93/125]) compared with reference trastuzumab (69.8% [90/129]) when administered as part of dual HER2-targeted therapy with pertuzumab plus chemotherapy in the neoadjuvant setting [17]. While larger prospective studies are required to confirm these findings, taken together with the 6-year time-to-event results from the present study and earlier findings from the CT-P6 3.2 study [3–5], these data support the biosimilarity of CT-P6 to reference trastuzumab in HER2-positive early breast cancer.

The introduction of biosimilars to reference trastuzumab such as CT-P6 increases the available avenues of treatment for patients with early HER2-positive breast cancer. Like most biologics, reference trastuzumab is more costly than traditional chemotherapy; despite improved effectiveness compared with chemotherapy alone, the increased costs may introduce financial barriers to accessing biologic treatment for some patients [18–21]. Reduced treatment costs, including those associated with biosimilar uptake, could both improve patient access to treatment and reduce the financial burden on healthcare systems [20, 22]. Indeed, a budget impact analysis conducted across France, Germany, Italy, Spain and the UK estimated 5-year savings of €19–172 million with the uptake of biosimilars to reference trastuzumab [23], whereas a larger analysis of CT-P6 for the treatment of breast cancer and gastric cancer conducted across 28 European countries estimated 5-year savings of €0.91–2.27 billion [24]. Real-world findings concur: in a retrospective analysis of 44 patients with HER2-positive early breast cancer, neoadjuvant CT-P6-based treatment was associated with cost savings of €1,474 per patient versus reference trastuzumab, with no difference in efficacy [25]. Lower cost, evidence of long-term clinical equivalence to reference products, and improved education and training are all factors that should influence the future adoption of anti-HER2 biosimilars [26, 27].

This was a multicentre study with a follow-up period of up to 6 years; however, the interpretation of our findings is limited because the study was not powered for survival analysis. Furthermore, data were collected retrospectively for the period between the end of the CT-P6 3.2 study and the start of the CT-P6 4.2 study, and long-term safety data were not collected.

5 Conclusions

Survival data from this extended follow-up of the CT-P6 3.2 study, until up to 6 years after enrolment in the original study, demonstrate the comparable long-term efficacy of CT-P6 and reference trastuzumab in patients with HER2-positive early breast cancer.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40259-023-00582-w.

Acknowledgements We thank all patients and investigators involved in the study. We thank Sinhye Kim and Ilsung Chang for their contributions to study design and data analysis/interpretation, and their review of the manuscript drafts. Medical writing support (including development of a draft outline and subsequent drafts in consultation with the authors, assembling tables and figures, collating author comments, copyediting, fact checking, and referencing) was provided by Beatrice Tyrrell, DPhil, CMPP, at Aspire Scientific (Bollington, UK), and funded by Celltrion, Inc. (Incheon, Republic of Korea).

Declarations

Funding This study was funded by Celltrion, Inc. (Incheon, Republic of Korea).

Conflicts of interest Justin Stebbing has received consulting fees or honoraria (2020–present) from Agenus, Alveo Technologies, APIM Therapeutics, Benevolent AI, Bryologyx, Celltrion, Certis, Eli Lilly, Equilibre Biopharmaceuticals, Graviton Bioscience Corporation, Greenmantle, Heat Biologics, IO Labs, Onconox, Pear Bio, Vaccitech, Volvox, vTv Therapeutics, and Zephyr AI; he has consulted with Lansdowne Partners and Vitruvian; he chairs the Board of Directors for Xerion and previously BB Biotech Healthcare Trust PLC; and is Editor-in-Chief of *Oncogene*. Taehong Park, Jaeyong Lee, Jiin Choi, Nahyun Kim, Keumyoung Ahn, Sang Joon Lee and Sunghyun Kim are employees of Celltrion, Inc. and hold stock in Celltrion, Inc. Eric Hyungseok Baek is an employee of Celltrion, Inc. Yauheni Baranau, Valery Baryash, Vladimir Moiseyenko, Dmytro Boliukh, Nicoleta Antone, Alexey Manikhas and Anatolii Chornobai have no conflicts of interest to disclose.

Availability of data and material All data generated or analysed during this study are included in this published article and its Online Supplementary Material.

Code availability Not applicable.

Authors' contributions Justin Stebbing, Taehong Park, Eric Hyungseok Baek, Keumyoung Ahn, Sang Joon Lee, and Sunghyun Kim contributed to study design and data analysis or interpretation. Yauheni Baranau, Valery Baryash, Vladimir Moiseyenko, Dmytro Boliukh, Nicoleta Antone, Alexey Manikhas, and Anatolii Chornobai contributed to data collection. Jaeyong Lee, Jiin Choi, and Nahyun Kim contributed to data analysis or interpretation. All authors reviewed and critically revised drafts of the manuscript, approved the version to be published, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics approval The study was conducted in accordance with the ethical principles originating in the Declaration of Helsinki, Good Clinical Practice, and all applicable laws or regulations. Before the start of the study, the protocol, informed consent form, advertisements to be used for the recruitment of study patients, and any other written information to be provided to the patients were approved by the institutional review board and/or independent ethics committee at each site (Table S1, OSM Resource 1).

Consent to participate Written informed consent was obtained from all individual participants included in the study.

Consent for publication All participants provided consent for their data to be published.

Prior presentation Selected data from the CT-P6 4.2 study were presented at the European Society for Medical Oncology (ESMO) Breast Cancer Congress (3–5 May 2022).

References

1. US Food and Drug Administration. Herzuma: prescribing information. 2019. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761091s001s002lbl.pdf. Accessed 6 Jan 2023.
2. European Medicines Agency. Herzuma: summary of product characteristics. 2022. https://www.ema.europa.eu/en/documents/product-information/herzuma-epar-product-information_en.pdf. Accessed 6 Jan 2023.
3. Stebbing J, Baranau Y, Baryash V, Manikhas A, Moiseyenko V, Dzagnidze G, et al. CT-P6 compared with reference trastuzumab for HER2-positive breast cancer: a randomised, double-blind, active-controlled, phase 3 equivalence trial. Lancet Oncol. 2017;18(7):917–28. https://doi.org/10.1016/S1470-2045(17)30434-5.
4. Esteva FJ, Baranau YV, Baryash V, Manikhas A, Moiseyenko V, Dzagnidze G, et al. Efficacy and safety of CT-P6 versus reference trastuzumab in HER2-positive early breast cancer: updated results of a randomised phase 3 trial. Cancer Chemother Pharmacol. 2019;84(4):839–47. https://doi.org/10.1007/s00280-019-03920-4.
5. Stebbing J, Baranau YV, Baryash V, Manikhas A, Moiseyenko V, Dzagnidze G, et al. Long-term efficacy and safety of CT-P6 versus trastuzumab in patients with HER2-positive early breast cancer: final results from a randomized phase III trial. Breast Cancer Res Treat. 2021;188(3):631–40. https://doi.org/10.1007/s10549-021-06240-5.
6. Jackisch C, Hegg R, Stroyakovskiy D, Ahn JS, Melichar B, Chen SC, et al. HannaH phase III randomised study: association of total pathological complete response with event-free survival in HER2-positive early breast cancer treated with neoadjuvant-adjuvant trastuzumab after 2 years of treatment-free follow-up. Eur J Cancer. 2016;62:62–75. https://doi.org/10.1016/j.ejca.2016.03.087.
7. de Azambuja E, Holmes AP, Piccart-Gebhart M, Holmes E, Di Cosimo S, Swaby RF, et al. Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): survival outcomes of a randomised, open-label, multicentre, phase 3 trial and their association with pathological complete response. Lancet Oncol. 2014;15(10):1137–46. https://doi.org/10.1016/S1470-2045(14)70320-1.
8. Ueno T, Masuda N, Sato N, Ohtani S, Yamamura J, Matsunami N, et al. Multicenter study of primary systemic therapy with docetaxel, cyclophosphamide and trastuzumab for HER2-positive operable breast cancer: the JBCRG-10 study. Jpn J Clin Oncol. 2020;50(1):3–11. https://doi.org/10.1093/jjco/hyz119.
9. Jackisch C, Stroyakovskiy D, Pivot X, Ahn JS, Melichar B, Chen SC, et al. Subcutaneous vs intravenous trastuzumab for patients with ERBB2-positive early breast cancer: final analysis of the HannaH Phase 3 randomized clinical trial. JAMA Oncol. 2019;5(5):e190339. https://doi.org/10.1001/jamaoncol.2019.0339.
10. Huober J, Holmes E, Baselga J, de Azambuja E, Untch M, Fumagalli D, et al. Survival outcomes of the NeoALTTO study (BIG 1–06): updated results of a randomised multicenter phase III neoadjuvant clinical trial in patients with HER2-positive primary breast cancer. Eur J Cancer. 2019;118:169–77. https://doi.org/10.1016/j.ejca.2019.04.038.
11. Piccart M, Procter M, Fumagalli D, de Azambuja E, Clark E, Ewer MS, et al. Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer in the APHINITY trial: 6 years' follow-up. J Clin Oncol. 2021;39(13):1448–57. https://doi.org/10.1200/JCO.20.01204.
12. Gligorov J, Pivot X, Ataseven B, De Laurentiis M, Jung KH, Manikhas A, et al. Safety and efficacy of adjuvant subcutaneous trastuzumab in human epidermal growth factor receptor 2-positive early breast cancer: final results of the SafeHER study. Breast. 2022;64:151–8. https://doi.org/10.1016/j.breast.2022.03.001.
13. Pivot X, Burian O, Bazan F, Wojtukiewicz M, Jang H, Kim S, et al. 154P Five-year follow-up of the phase III study comparing SB3 (trastuzumab biosimilar) and reference trastuzumab in patients with HER2 positive early or locally advanced breast cancer [abstract]. Ann Oncol. 2021;32(suppl 5):S428. https://doi.org/10.1016/j.annonc.2021.08.435.
14. Dackus G, Jozwiak K, van der Wall E, van Diest PJ, Hauptmann M, Siesling S, et al. Concurrent versus sequential use of trastuzumab and chemotherapy in early HER2+ breast cancer. Breast Cancer Res Treat. 2021;185(3):817–30. https://doi.org/10.1007/s10549-020-05978-8.
15. Yamashiro H, Iwata H, Masuda N, Yamamoto N, Nishimura R, Ohtani S, et al. Outcomes of trastuzumab therapy in HER2-positive early breast cancer patients: extended follow-up of JBCRG-cohort study 01. Breast Cancer. 2020;27(4):631–41. https://doi.org/10.1007/s12282-020-01057-4.
16. Gianni L, Pienkowski T, Im YH, Tseng LM, Liu MC, Lluch A, et al. 5-year analysis of neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer (NeoSphere): a multicentre, open-label, phase 2 randomised trial. Lancet Oncol. 2016;17(6):791–800. https://doi.org/10.1016/S1470-2045(16)00163-7.
17. Bae SJ, Kim JH, Ahn SG, Jeung HC, Sohn J, Kim GM, et al. Real-world clinical outcomes of biosimilar trastuzumab (CT-P6) in HER2-positive early-stage and metastatic breast cancer. Front Oncol. 2021;11:689587. https://doi.org/10.3389/fonc.2021.689587.
18. Seferina SC, Ramaekers BLT, de Boer M, Dercksen MW, van den Berkmortel F, van Kampen RJW, et al. Cost and cost-effectiveness of adjuvant trastuzumab in the real world setting: a study of the Southeast Netherlands Breast Cancer Consortium. Oncotarget. 2017;8(45):79223–33. https://doi.org/10.18632/oncotarget.16985.

19. Aboutorabi A, Hadian M, Ghaderi H, Salehi M, Ghiasipour M. Cost-effectiveness analysis of trastuzumab in the adjuvant treatment for early breast cancer. Glob J Health Sci. 2014;7(1):98–106. https://doi.org/10.5539/gjhs.v7n1p98.
20. Gupta N, Verma RK, Gupta S, Prinja S. Cost effectiveness of trastuzumab for management of breast cancer in India. JCO Glob Oncol. 2020;6:205–16. https://doi.org/10.1200/JGO.19.00293.
21. Li J, Wang S, Wang Y, Wang X, Wang H, Feng J, et al. Disparities of trastuzumab use in resource-limited or resource-abundant regions and its survival benefit on HER2 positive breast cancer: a real-world study from China. Oncologist. 2017;22(11):1333–8. https://doi.org/10.1634/theoncologist.2017-0088.
22. Kvien TK, Patel K, Strand V. The cost savings of biosimilars can help increase patient access and lift the financial burden of health care systems. Semin Arthritis Rheum. 2022;52:151939. https://doi.org/10.1016/j.semarthrit.2021.11.009.
23. Jang M, Simoens S, Kwon T. Budget impact analysis of the introduction of rituximab and trastuzumab intravenous biosimilars to EU-5 markets. BioDrugs. 2021;35(1):89–101. https://doi.org/10.1007/s40259-020-00461-8.
24. Lee SM, Jung JH, Suh D, Jung YS, Yoo SL, Kim DW, et al. Budget impact of switching to biosimilar trastuzumab (CT-P6) for the treatment of breast cancer and gastric cancer in 28 European countries. BioDrugs. 2019;33(4):423–36. https://doi.org/10.1007/s40259-019-00359-0.
25. Bernat-Peguera A, Trigueros M, Ferrando-Diez A, Ibanez C, Bystrup S, Martinez-Cardus A, et al. Efficacy of CT-P6 (trastuzumab biosimilar) versus reference trastuzumab in combination with pertuzumab in HER2-positive early-stage breast cancer: preclinical and real-life clinical data. Breast. 2022;62:1–9. https://doi.org/10.1016/j.breast.2022.01.007.
26. Lammers P, Criscitiello C, Curigliano G, Jacobs I. Barriers to the use of trastuzumab for HER2+ breast cancer and the potential impact of biosimilars: a physician survey in the United States and emerging markets. Pharmaceuticals (Basel). 2014;7(9):943–53. https://doi.org/10.3390/ph7090943.
27. Triantafyllidi E, Triantafillidis JK. Systematic review on the use of biosimilars of trastuzumab in HER2+ breast cancer. Biomedicines. 2022;10(8):2045. https://doi.org/10.3390/biomedicines10082045.

Authors and Affiliations

Justin Stebbing[1,2,3] · Yauheni Baranau[4] · Valery Baryash[4] · Vladimir Moiseyenko[5] · Dmytro Boliukh[6] · Nicoleta Antone[7] · Alexey Manikhas[8] · Anatolii Chornobai[9] · Taehong Park[10] · Eric Hyungseok Baek[10] · Jaeyong Lee[11] · Jiin Choi[11] · Nahyun Kim[11] · Keumyoung Ahn[10] · Sang Joon Lee[12] · Sunghyun Kim[13]

✉ Sunghyun Kim
sunghyun.kim@celltrion.com

1 Department of Surgery and Cancer, Imperial College London, London, UK

2 School of Life Sciences, Anglia Ruskin University, Cambridge, UK

3 Oncogene, London, UK

4 Chemotherapy Department 1, Minsk City Clinical Cancer Center, Minsk, Belarus

5 Oncology Department, St. Petersburg Clinical Scientific and Practical Centre of Specialized Kinds of Medical Care, St. Petersburg, Russian Federation

6 Chemotherapy Department, Vinnytsya Regional Clinical Oncology Dispensary, Vinnytsya, Ukraine

7 Radiotherapy I Department, IOCN-The Oncology Institute "Prof. Dr. Ion Chiricuta", Cluj-Napoca, Romania

8 Oncology Department, City Clinical Oncological Dispensary, St. Petersburg, Russian Federation

9 Chemotherapy Department, Poltava Regional Clinical Oncology Center, Poltava, Ukraine

10 Clinical Planning, Celltrion, Inc., Incheon, Republic of Korea

11 Biometrics, Celltrion, Inc., Incheon, Republic of Korea

12 Data Science Institute, Celltrion, Inc., Incheon, Republic of Korea

13 Medical Science Division, Celltrion, Inc., 23, Academy-ro, Yeonsu-gu, Incheon 22014, Republic of Korea