3-year follow-up of a phase III trial comparing the efficacy and safety of neoadjuvant and adjuvant trastuzumab and its biosimilar CT-P6 in HER2 positive early breast cancer (EBC)

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BACKGROUND

- Trastuzumab is a recombinant humanized monoclonal antibody which is designed to target the human epidermal growth factor receptor 2 (HER2).
- CT-P6 has an identical amino acid sequence and highly similar physicochemical and in vitro functional properties to trastuzumab.
- The primary endpoint of this phase 3 trial (NCT02162667), pathological complete response (pCR) rate was entirely within the pre-defined equivalence margin (Lancet Oncol 2017).
- Safety and efficacy at 1 year (ESMO 2017), and cardiac toxicity at a median of 19 months (SABCS 2017) and efficacy and safety at 2 years (SABCS 2018) were similar between the two treatment groups.
- The long term efficacy endpoints (disease-fee survival [DFS], overall survival [OS]) and cardiotoxicity with a median follow-up of 3 years were investigated.
- CT-P6 was approved by both US FDA and European Commission as a biosimilar to reference trastuzumab (RTZ).

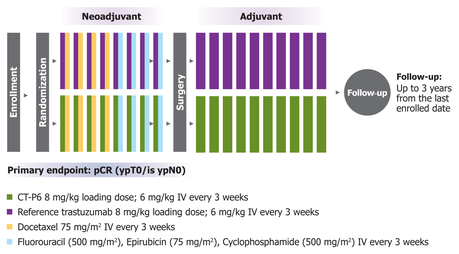
OBJECTIVES

- In addition to primary endpoint (demonstration of therapeutic equivalence of CT-P6 and RTZ as determined by pCR [ypT0/is ypN0], time to event analyses as secondary efficacy endpoints and cardiac safety were assessed.

METHOD

- Female patients with HER2+ early breast cancer with
  - aged ≥ 18 years
  - clinical stage I–IIIa (Breast Cancer Staging 7th edition of AJCC)
  - LVEF ≥ 55%
  - no serious cardiac illness
    (New York Heart Association [NYHA] class ≤1, no history of congestive heart failure [CHF])
- Received 8 cycles of study drug with docetaxel and FEC as Neoadjuvant treatment and up to 1 year (or 10 cycles) monotherapy as Adjuvant treatment then followed up for up to 3 years from the last enrolled date (Figure 1).
- Data are presented as of data cut off October 23, 2018 (Median follow-up of 39 months).

Figure 1. Study Design

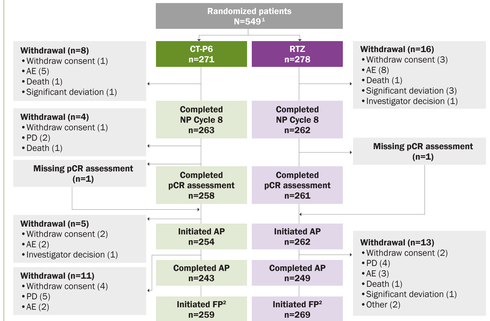


RESULTS

Patient Disposition and Demographic Characteristics

- A total of 549 patients were randomized at 112 centers in 22 countries (CT-P6 = 271; RTZ = 278) and 492 patients completed 1 year of treatment.
- A total of 519 patients (CT-P6 = 258; RTZ = 261) completed pCR assessment.
- A total of 528 patients (CT-P6 = 259; RTZ = 269) initiated the Follow-Up Period, regardless of completion of treatment (Figure 2).
- Patient characteristics were similar between the two treatment groups (Table 1).

Figure 2. Patients Disposition



Abbreviations: AE, adverse event; AP, Adjuvant Period, FP, Follow-Up Period; GCP, good clinical practice; NP, neoadjuvant period; pCR, pathological complete response; PD, progressive disease.
1. Thirteen patients of 1 site were excluded from all population due to GCP noncompliance.
2. The patients were entered into the post-treatment Follow-Up Period regardless of completion of treatment if they did not withdraw consent.

Table 1: Patient Characteristics

Characteristic, n (%)		CT-P6 (N = 271)	RTZ (N = 278)
Age	Median (range)	53.0 (24 - 78)	53.0 (22 - 74)
ECOG PS	0	239 (88.2)	250 (89.9)
	1	32 (11.8)	28 (10.1)
Disease Stage	I	23 (8.5)	31 (11.2)
	IIa	75 (27.7)	86 (30.9)
	IIb	105 (38.7)	98 (35.3)
	IIIa	64 (23.6)	61 (21.9)
	IIIb[1]	1 (0.4)	0
	IIIc[1]	3 (1.1)	1 (0.4)
	IV[1]	0	1 (0.4)
Hormone Status	Positive[2]	160 (59.0)	162 (58.3)
	Negative	111 (41.0)	116 (41.7)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group perfomance status.
[1]Due to ineligibility, 6 patients were excluded from Per Protocol Set.
[2]If estrogen and/or progesterone status is positive, hormone status is positive.

EFFICACY RESULTS

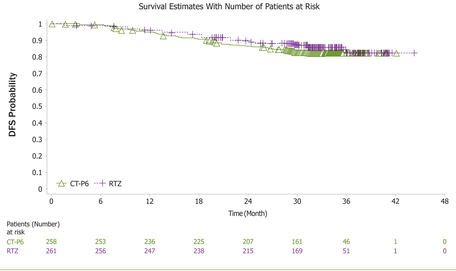
- Median Follow-Up Period was 39.1 months (CT-P6: 38.7 months, RTZ: 39.6 months).
- The median time for DFS and OS is not reached yet, however, the Kaplan-Meier curves of DFS and OS are similar between two treatment groups (Figure 3).
- The proportion of DFS events and OS events were comparable in the PPS (per-protocol set) and ITT (Intent-to-Treat) set (Table 2).

Table 2: Summary of Long Term Efficacy Endpoints

	ITT Set[1]		PPS	
	CT-P6 (N = 258)	RTZ (N = 261)	CT-P6 (N = 248)	RTZ (N = 256)
DFS rate				
1 year (95% CI)	0.95 (0.91, 0.97)	0.96 (0.93, 0.98)	0.95 (0.91, 0.97)	0.96 (0.93, 0.98)
2 years (95% CI)	0.87 (0.82, 0.90)	0.89 (0.85, 0.93)	0.87 (0.81, 0.90)	0.89 (0.85, 0.92)
3 years (95% CI)	0.83 (0.77, 0.87)	0.83 (0.76, 0.88)	0.82 (0.77, 0.87)	0.82 (0.75, 0.88)
Hazard ratio (95% CI)	1.23 (0.78, 1.93)		1.23 (0.78, 1.94)	
p-value	0.3807		0.3808	
	ITT Set		**PPS**	
	CT-P6 (N = 271)	RTZ (N = 278)	CT-P6 (N = 248)	RTZ (N = 256)
OS rate				
1 year (95% CI)	0.99 (0.97, 1.00)	0.99 (0.97, 1.00)	1.00 (1.00, 1.00)	1.00 (0.97, 1.00)
2 years (95% CI)	0.97 (0.93, 0.98)	0.98 (0.96, 0.99)	0.98 (0.95, 0.99)	0.98 (0.96, 0.99)
3 years (95% CI)	0.93 (0.90, 0.96)	0.94 (0.90, 0.96)	0.95 (0.91, 0.97)	0.94 (0.90, 0.96)
Hazard ratio (95% CI)	1.10 (0.57, 2.13)		0.87 (0.42, 1.82)	
p-value	0.7710		0.7181	

1. Only surgery underwent patients are included in the analysis.

Figure 3: Kaplan-Meier Plot of Long Term Efficacy



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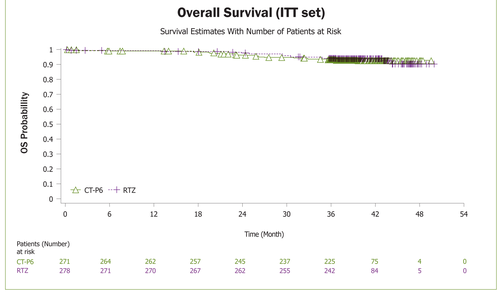


Cardiotoxicity Results

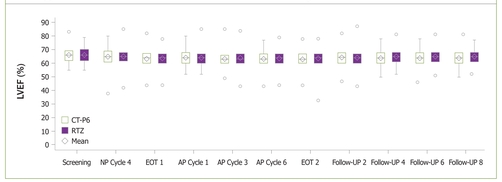
- The mean LVEF value was maintained over 60% during 1-year treatment and Follow-Up Period (Figure 4).
- For the overall worst value of LVEF, majority of patients showed increase, no change or decreased <10 points from baseline.
- Significant LVEF decrease was similar between the 2 treatment groups [9 (3.3%) patients in the CT-P6 treatment group and 7 (2.5%) patients in the RTZ group]. With the exception of 1 patient who was terminated due to congestive cardiomyopathy, all 15 patients had no signs and symptoms (Table 3).

Table 3. Summary of Left Ventricular Ejection Fraction, Overall Worst Value

Visit Results	CT-P6 (N = 271)	RTZ (N = 278)
Baseline		
Median	66.00	66.00
Range	55.0 – 83.0	55.0 – 79.0
Overall (Post-baseline Worst Value)		
Median	60.00	60.00
Range	38.0 - 70.0	30.0 - 76.0
Increase, no change, or decrease of <10 points from baseline	184 (67.9%)	199 (71.6%)
Decrease of ≥ 10 points	83 (30.6%)	73 (26.3%)
LVEF <50 and decrease of ≥ 10 points	9 (3.3%)	7 (2.5%)

Abbreviation: LVEF, left ventricular ejection fraction.

Figure 4. Box-Plot of Mean Left Ventricular Ejection Fraction Over Time



Abbreviation: AP, Adjuvant Period; EOT1, first end-of-treatment visit; EOT2, second end-of-treatment visit; LVEF, left ventricular ejection fraction; NP, Neoadjuvant Period.

Cardiac Safety Results

- Treatment emergent adverse events (TEAE) of cardiac disorders were reported to be similar between the 2 treatment groups (Table 4).
- After the completion of 1-year treatment, cardiac safety was tolerable. During the Follow-Up Period, < 2% of patients were reported to have a cardiac adverse event (3 [1.1%] patients in the CT-P6 group and 3 [1.1%] patient in the RTZ group).

Table 4. Summary of Cardiac Adverse Events Over 1-Year Treatment and Follow-Up Period

System Organ Class Preferred Term	CT-P6 (N = 271)	RTZ (N = 278)
Cardiac disorders	32 (11.8%)	39 (14.0)
Related	22 (8.1%)	24 (8.6%)
Grade 1	19 (7.0%)	16 (5.8%)
Grade 2	2 (0.7%)	7 (2.5%)
Grade 3	1 (0.4%)	0
Grade 5[1]	0	1 (0.4%)
Unrelated	14 (5.2%)	20 (7.2%)
Grade 1	9 (3.3%)	16 (5.8%)
Grade 2	5 (1.8%)	3 (1.1%)
Grade 4	0	1 (0.4%)
Cardiac disorders reported ≥1%		
Cardiomyopathy	1 (0.4%)	5 (1.8%)
Mitral valve incompetence	3 (1.1%)	4 (1.4%)
Palpitations	10 (3.7%)	8 (2.9%)
Sinus tachycardia	2 (0.7%)	3 (1.1%)
Tachycardia	6 (2.2%)	5 (1.8%)

1. Acute myocardial infarction

CONCLUSION

- The long term efficacy in terms of DFS and OS was comparable between CT-P6 and RTZ.
- In addition to the pCR equivalence, this study results further supported the similarity of CT-P6 to RTZ through DFS and OS.
- CT-P6 was consistently well tolerated with a similar cardiotoxicity profile to that of RTZ through long duration (over 3 years) of follow-up.

REFERENCE

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