

OF TRASTUZUMAB (HERCEPTIN®) PLUS DOCETAXEL WITH OR WITHOUT CARBOPLATIN AS FIRST-LINE THERAPY IN HER2-AMPLIFIED METASTATIC BREAST CANCER

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ABSTRACT

Background: Based on preclinical synergy between docetaxel (T), carboplatin (C) and trastuzumab (H), BCIRG conducted a Phase III trial with HER2+ MBC to evaluate efficacy and safety of H in combination with T or TC. **Methods:** 263 patients (pts) with HER2 FISH+ MBC were randomised to TH (H with T 100 mg/m²) or TCH (H with T 75 mg/m² and C AUC=6). Chemo was given q3 wks for 8 cycles with wly H at 2 mg/kg (loading dose of 4 mg/kg), followed by H q3 wks at 6 mg/kg until progression. Pts were stratified by centre and prior (neo)adjuvant taxane chemo. Primary end point was TTP. Secondary end points include overall survival, response rate, duration of response (DR), clinical benefit (CB) and safety. **Results:** 131 pts were treated in each arm. Pt characteristics were well balanced in both groups. Importantly, only 52% of pts received C at the protocol-specified dose (RDI >0.9). Efficacy analysis was conducted at 204 events. There was no significant difference between TH and TCH in median TTP (11.1 vs 10.4 mos, p=0.57), ORR (73% in both arms), DR (10.7 vs 9.4 mos) and CB (67% in both arms). Median survival in both arms exceeded 40 months. The grade 3/4 toxicities were: infection (29% vs 22.9%), neutropenic infection (16.8% vs 9.2%), thrombocytopenia (2% vs 15%), febrile neutropenia (12% vs 13%), asthenia (5% vs 12%), anaemia (5% vs 11%). Two pts died (1.5%) due to sepsis in TCH. Absolute LVEF decline >15% was seen in 5.5% vs 6.7% of pts. One pt (0.8%) had a symptomatic CHF in TH arm. **Conclusion:** Both TH and TCH are highly effective treatment regimens in women having HER2+ MBC, with median survival exceeding 40 months in each arm.

INTRODUCTION

- Approximately 25% of breast cancer tumours exhibit human epidermal growth factor receptor 2 (HER2) amplification, which is associated with a poor clinical outcome for patients.^{1,3} Trastuzumab (Herceptin®; H), a monoclonal antibody against HER2, improves survival in women with metastatic breast cancer when given as monotherapy^{4,5} or in combination with chemotherapy.^{6,7}
- Preclinical studies indicate that docetaxel (Taxotere®; T) and platinum salts are highly synergistic when combined with H. In two Phase II studies, this triple combination resulted in response rates of 58-79% and longer time to progression in patients with HER2-positive advanced breast cancer.⁸
- In a randomised Phase III study of H and paclitaxel (P) with or without carboplatin (C) as first-line therapy for women with HER2-positive metastatic breast cancer, the addition of C to PH significantly improved response rates (52% vs 36%; p=0.04) and progression-free survival (10.7 vs 7.1 months; p=0.03).⁹
- In a randomised Phase II study of T with or without H as first-line therapy for women with HER2-positive metastatic breast cancer, the addition of H significantly improved response rates (61% vs 34%; p=0.0002), time to progression (median 11.7 vs 6.1 months; p=0.0001) and overall survival (median 31.2 vs 22.7 months; p=0.0325).

OBJECTIVE

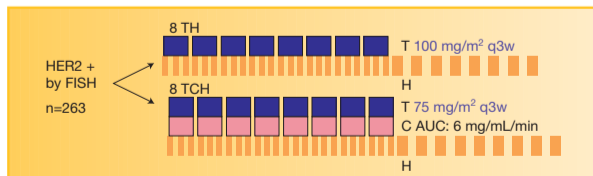
- The randomised, Phase III, BCIRG 007 trial was initiated to evaluate the efficacy and safety of TCH compared with TH as first-line therapy for women with HER2-positive metastatic breast cancer.

METHODS

Study design

- This was a multicentre, prospective, non-blinded, randomised, Phase III trial in women aged ≥18 years with HER2-positive (confirmed by fluorescence *in situ* hybridisation [FISH]) metastatic breast cancer.
- Eligible patients had either measurable or non-measurable lesions according to Response Evaluation Criteria In Solid Tumors, a Karnofsky performance status index ≥60%, normal cardiac function confirmed by left ventricular ejection fraction (LVEF) [lower limit of normal], adequate haematological, hepatic and renal function, and no prior chemotherapy for their locally advanced or metastatic disease.
- Patients were stratified at inclusion according to centre and prior adjuvant/neoadjuvant chemotherapy, and then randomly assigned to receive TH or TCH until disease progression, second primary malignancy or unacceptable toxicity (Figure 1). Study treatments were as follows:
 - TH: T single agent 100 mg/m² q3w x 8 cycles. H 4 mg/kg intravenous (iv) loading dose administered on Day 1 of Cycle 1, followed by 2 mg/kg iv weekly starting on Day 8 during chemotherapy. Three weeks after the last infusion of chemotherapy, H (6 mg/kg iv) was administered q3w
 - TCH: T 75 mg/m² and C at target AUC=6 mg/mL/min q3w x 8 cycles. H was administered as in the TH arm.

Figure 1. Study design



End points

- The primary efficacy end point was time to progression. Secondary efficacy end points included evaluation of clinical benefit, response rate, duration of overall response and overall survival.
- Safety was assessed based on the incidence of adverse events (AEs) and serious AEs, haematological and biochemical laboratory values, and cardiac monitoring via LVEF and clinical assessments.

Statistical analysis

- All efficacy analyses were performed on randomised patients who received study medication at least once (intent-to-treat population). All safety analyses were performed according to the actual study medication received. Assuming an absolute improvement of 50% in time to progression (TH: 7 months; TCH: 10.5 months), with 80% power and a 2-sided significance level of 5%, a sample size of 125 patients per arm was required, with 204 events occurring for the final analysis.

RESULTS

Patient demographics and disposition

- Overall, 263 HER2-positive (FISH+) women were randomised into the study: 131 in the TH arm and 132 in the TCH arm. One patient in the TCH arm did not receive study drug and was excluded from analyses. The baseline patient demographics of both treatment groups were well balanced (Table 1).

Table 1. Baseline patient demographics

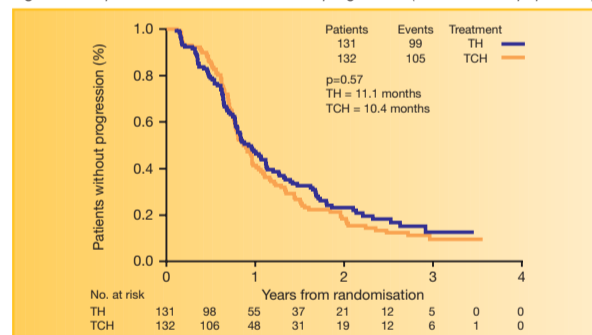
Characteristic	TH (n=131)	TCH (n=132)
Age <50 years, n (%)	49 (37.4)	61 (46.2)
Karnofsky performance status, %	90	100
Disease status, n (%)		
Locally advanced	3 (2.3)	2 (1.5)
Metastatic	128 (97.7)	130 (98.5)
ER+ and/or PgR+, n (%)	95 (72.5)	86 (65.2)
Extent of disease, n (%)		
1 or 2 organs	70 (53.4)	72 (54.5)
Disease involvement, n (%)		
Visceral	87 (66.4)	77 (58.3)
Liver	67 (51.1)	65 (49.2)
Bone	55 (42.0)	44 (33.3)
Prior systemic treatments, n (%)		
Endocrine	35 (26.7)	48 (36.4)
Prior chemotherapy	73 (55.7)	71 (53.8)
Prior chemotherapy with taxane	14 (10.7)	12 (9.1)
Prior anthracycline	43 (32.8)	43 (32.6)
ER, oestrogen receptor; PgR, progesterone receptor.		

- The maximum number of chemotherapy cycles (8) was received by 80 (61.1%) and 95 (72%) patients in the TH and TCH arms, respectively.
- Overall, 51 patients in the TH arm discontinued treatment for the following reasons: disease progression (25 patients); non-cardiac AEs (17); cardiac AEs (1); withdrawal of consent (3); death (2); other (3). In the TCH arm, 37 patients discontinued for: disease progression (20 patients); non-cardiac AEs (10); withdrawal of consent (2); death (3); other (2).

Efficacy

- At a median follow-up of 27.5 months in the TH arm and 27.8 months in the TCH arm, 204 events (TH: 99; TCH: 105) had occurred in the trial.
- Median time to progression was 11.1 months in the TH arm, compared with 10.4 months in the TCH arm (p=0.57) [Figure 2].

Figure 2. Kaplan-Meier estimate of time to progression (intent-to-treat population)



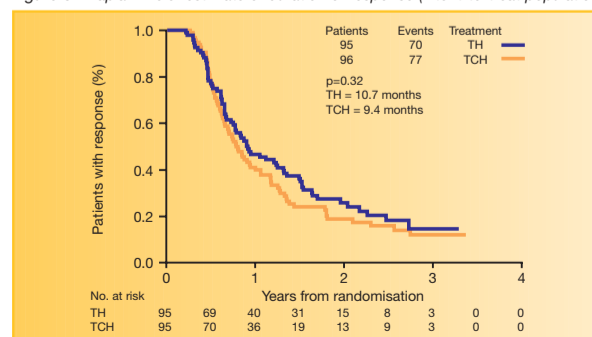
- Similar response rates of 73% were observed for patients in both treatment arms, with similar numbers of patients experiencing a complete response, partial response or stable disease. Clinical benefit was seen in 88 (67%) patients in each arm (Table 2).

Table 2. Response rates and clinical benefit

	TH (n=131)	TCH (n=131)
Best overall response, n (%)		
Complete response	24 (18.3)	23 (17.6)
Partial response	71 (54.2)	73 (55.7)
Stable disease	24 (18.3)	20 (15.3)
Progressive disease	11 (8.4)	11 (8.4)
Not evaluable	1 (0.8)	5 (3.8)
Response rate, % (95% CI)	73 (64, 80)	73 (64.3, 80.1)
Clinical benefit rate, n (%)	88 (67.2)	88 (67.2)

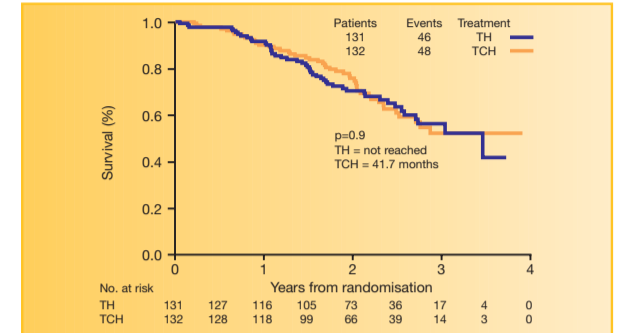
- The median duration of response was 10.7 months (95% confidence interval [CI]: 9.0, 15.8) in the TH arm, compared with 9.4 months (95% CI: 7.8, 12.0) in the TCH arm (p=0.32) [Figure 3].

Figure 3. Kaplan-Meier estimate of duration of response (intent-to-treat population)



- Interim analysis of overall survival did not show any significant difference between the two treatment arms, with 46 and 48 deaths in the TH and TCH arms, respectively (Figure 4). Median overall survival was 41.7 months in the TCH arm (not yet reached in the TH arm).

Figure 4. Kaplan-Meier estimate of overall survival (intent-to-treat population)



Safety

- Non-haematological toxicities (both overall and grade 3/4) were reported more frequently for patients in the TH arm compared with the TCH arm. The most common treatment-related non-haematological toxicities were alopecia, asthenia and gastrointestinal disorders (including nausea, vomiting, diarrhoea, stomatitis and constipation) [Table 3].

Table 3. Non-haematological toxicities (overall)

	No. patients (%)		p value
	TH (n=131)	TCH (n=131)	
Neuropathy			
Sensory	75 (57.3)	58 (44.3)	0.048
Motor	12 (9.2)	4 (3.1)	0.068
Myalgia	58 (44.3)	41 (31.3)	0.041
Peripheral oedema	52 (39.7)	38 (29.0)	
Rash/desquamation	42 (32.1)	20 (15.3)	0.002
Nail changes	72 (55.0)	43 (32.8)	<0.001
Gastrointestinal			
Nausea	70 (53.4)	96 (73.3)	
Vomiting	37 (28.2)	58 (44.3)	

- Grade 3/4 haematological toxicities occurred in a similar proportion of patients in both treatment arms, with the exception of neutropenic infection, which occurred more often in patients receiving TH, and thrombocytopenia, which occurred significantly more often in patients receiving TCH (Table 4).

Table 4. Grade 3/4 haematological toxicities

AE	No. patients (%)		p value
	TH (n=131)	TCH (n=131)	
Infection	38 (29)	30 (22.9)	0.324
Neutropenic infection	22 (16.8)	12 (9.2)	0.097
Febrile neutropenia	16 (12.2)	17 (13)	
Anaemia	7 (5.3)	14 (10.7)	
Thrombocytopenia	3 (2.3)	20 (15.3)	<0.001
Septic death	0	2 (1.5)	

- No new or unexpected AEs related to cardiac toxicity occurred in either treatment arm. The incidence of cardiac events in each arm remained at an acceptable level (Table 5). One patient (0.8%) in the TH arm experienced symptomatic congestive heart failure.

Table 5. Cardiac toxicity

	TH (n=131)	TCH (n=131)
Cardiac left ventricular function, n (%)		
Grade 1	6 (4.6)	6 (4.6)
Grade 2	4 (3.1)	6 (4.6)
Grade 3	1 (0.8)	0
Grade 4	0	0
Absolute LVEF decline, n (%)		
0-10 points and <LLN	4 (3.1)	5 (3.8)
11-15 points and <LLN	3 (2.3)	3 (2.3)
>15 points and <LLN	7 (5.3)	8 (6.1)
LLN, lower limit of normal.		

CONCLUSIONS

- Both TH and TCH were highly effective therapies in this population of patients with HER2-positive metastatic breast cancer, demonstrating high response rates, median time to progression of >10 months and median overall survival of >40 months.
- No significant differences in efficacy were obtained by the addition of C; however, the T dose level was different between the two arms (100 and 75 mg/m² for TH and TCH, respectively).
- TH and TCH were well tolerated but had different safety profiles:
 - TH was associated with more episodes of neuropathy, myalgia, skin and nail changes, and neutropenic infections
 - TCH was associated with more episodes of thrombocytopenia, nausea and vomiting.
- Cardiac toxicity was not a significant safety issue in either treatment arm.

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