BCIRG 007 study

A multicenter phase III randomized trial comparing docetaxel and trastuzumab with docetaxel, carboplatin and trastuzumab first line chemotherapy for patients with metastatic breast cancer containing the Her2neu alteration

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On behalf of the BCIRG 007 Investigators

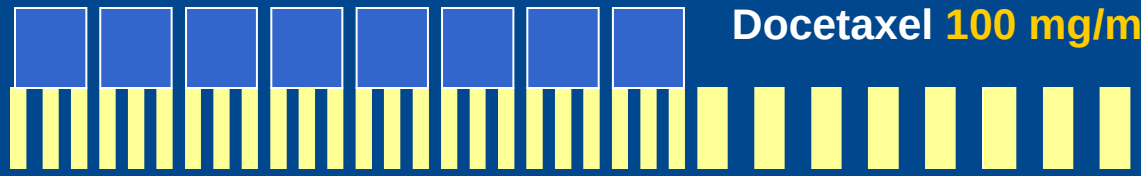
BCIRG 007

First Line Metastatic Breast Cancer

HER2 +
by FISH

N = 263

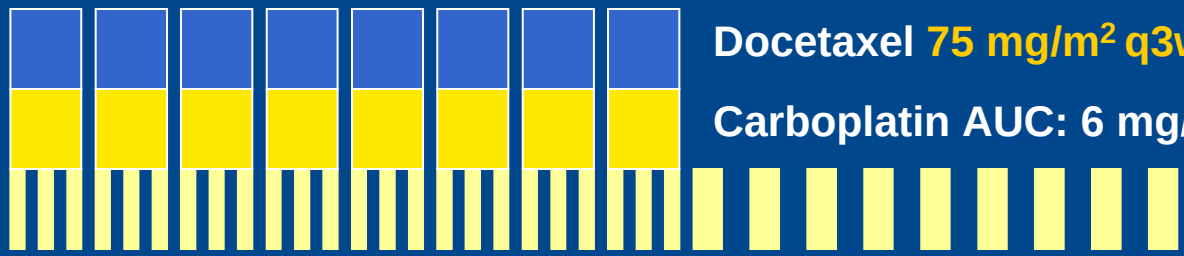
8 TH



Docetaxel 100 mg/m² q3w

Trastuzumab

8 TCH



Docetaxel 75 mg/m² q3w

Carboplatin AUC: 6 mg/ml/min

Trastuzumab

Stratification:

- Prior CT: adjuvant and/or neoadjuvant
- Center

Endpoints

Primary

- Time to Disease Progression

Secondary

- RR, Duration of OR, Clinical Benefit
- Toxicity
- Overall Survival
- Pathologic & Molecular Markers

Protocol Assumptions

Her2+ (FISH) metastatic pts

- Median TTP **TH**: 7.0 months
- Median TTP **TCH**: 10.5 months

(50% Improvement)

- Number of events for final analysis: **204**

(significance = 0.05, power = 0.8)

Protocol Defined Analyses

All efficacy analyses according to ITT (all randomized patients)

All safety analyses according to treatment actually received

- Toxic deaths
- Cardiac toxicity : LVEF and clinical

Patient Characteristics

Randomised (n = 263)	TH (n = 131)	TCH (n = 132)
Eligible	125 (95.4%)	128 (97%)
Treated	131 (100%)	131 (99.2%)
Age < 50	49 (37.5%)	61 (46.3%)
KPS	90	100
Prior Systemic Treatments:		
Endocrine	35 (26.7%)	48 (36.4%)
Chemotherapy (adj):	73 (55.7%)	71 (53.8%)
No prior CT	57 (43.5%)	59 (44.7%)
Prior CT without Tax	60 (45.8%)	61 (46.2%)
Prior CT with Taxane	14 (10.7%)	12 (9.1%)
Prior Anthracycline	43 (32.8)	43 (32.6)

Tumor Characteristics

Randomized (n=263)	TH n=131	TCH n=132
ER and/or PgR+	95 (72.5%)	86 (65.2%)
Extent of Disease		
1 or 2 organs	70 (53.4%)	72 (54.5%)
More than 2	61(46.6%)	60 (45.5%)
Disease Involvement		
Visceral involvement	87 (66.4%)	77 (58.3%)
Liver involvement	67 (51.1%)	65 (49.2%)
Bone involvement	55 (41.9%)	44 (33.3%)
Disease status at study entry		
Locally Advanced	3 (2.3%)	2 (1.5%)
Metastatic	128 (97.7%)	130 (98.5)

Exposure to Treatment

Treated (n=262)	TH n=131	TCH n=131
Completed 8 cycles	84 (64.1%)	103 (78.6%)
Relative dose intensity		
Tax > 0.9	106 (80.9%)	99 (75.6%)
Relative dose intensity		
Carbo > 0.9	-	67 (51.9%)

2 Patients received Cisplatin: Relative Dose intensity: both > 0.9

Chemotherapy discontinuation

Treated (n=262)	TH n=131	TCH n=131
Received max no of cycles	80 (61.1%)	95 (72%)
Discontinued:		
Disease progression	25 (19.1%)	20 (15.2%)
Adverse Events non cardiac	17 (13%)	10 (7.6%)
Adverse Events cardiac	1 (2.3%)	0 (0%)
Consent withdrawn	3 (0.8%)	2 (1.5%)
Death (5)	2 (1.5%)	3 (2.3%)
• Septic	0 (0%)	2 (1.5%)
• Non septic	1 (0.8%)	0 (0.0%)
• Breast cancer	0 (0.0%)	1 (0.8%)
• Other	1 (0.8%)	0 (0.0%)

Docetaxel: Reduction during Chemotherapy

Treated (n=262)	TH n=131	TCH n=131
Number with dose reduction	27 (20.6%)	26 (19.8%)
Reasons		
- Hematol toxicity	11 (40.7%)	13 (50%)
- Non-Hematol toxicity	16 (59.2%)	9 (34.6%)
- Hematol and Non-Hematol	0 (0%)	1 (3.8%)
- Other	2 (7.4%)	0 (0%)

Missing data for 4 pts with a dose higher than the recommended at cycle 1

Carboplatin: Reduction during Chemotherapy (TCH)

	TCH n=129
Reasons – reduction due to toxicity	
- Hematology toxicity	8 (8.9%)
- Non-Hematology toxicity	2 (2.2%)
- Hematology and Non-Hematology toxicity	2 (2.2%)
- Other	2 (2.2%)

Efficacy Analysis
(cutoff date Dec 26, 2005)

- Median follow-up:

  TH: 27.5 mos vs

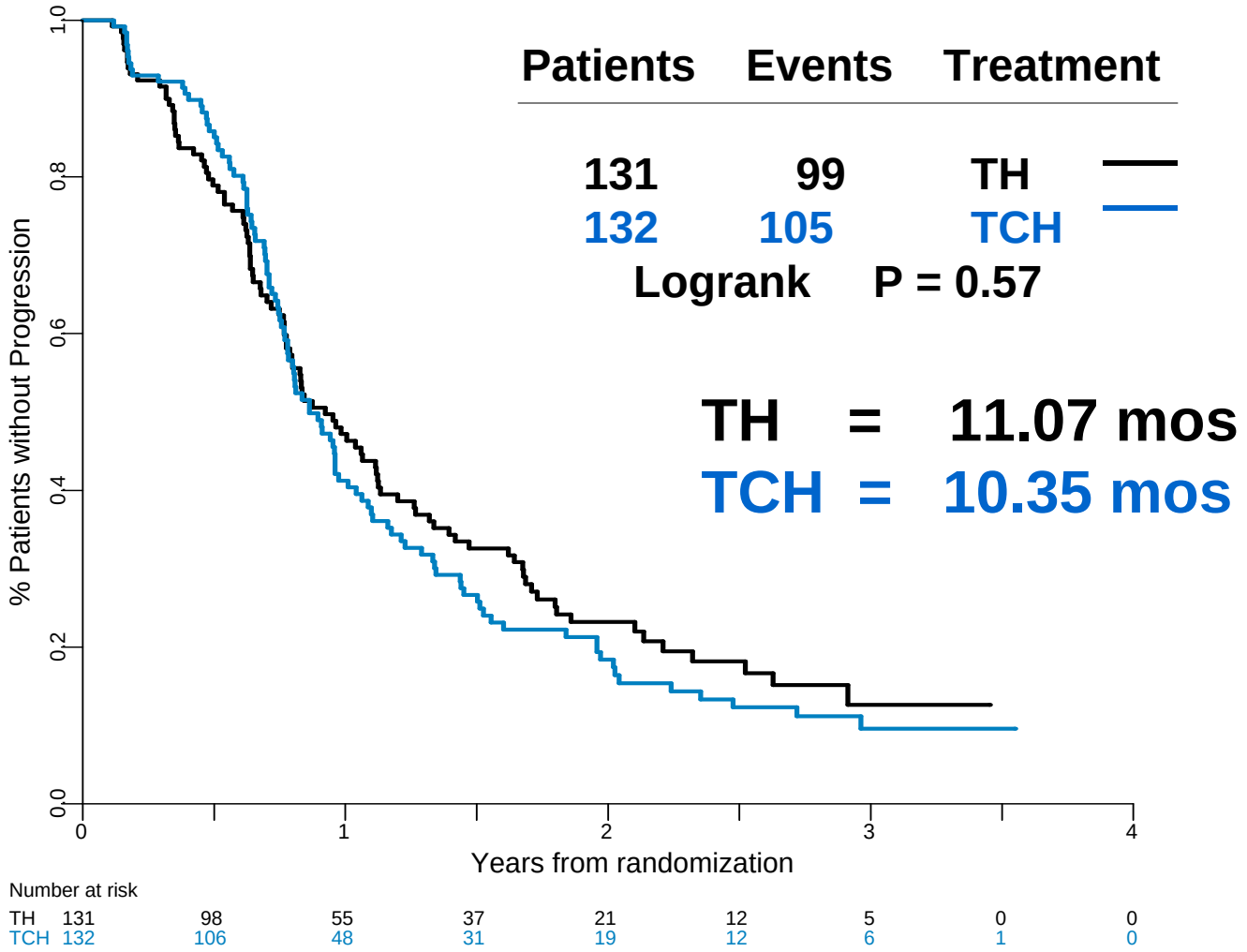
  TCH: 27.8 mos

- Events: 204
- Deaths: 94

Efficacy Analysis: TTP

Number of events	TH n=131	TCH n=132	All n=263
Total number of patients with an event	99	105	204
Disease Progression	98	105	203
Second Primary Malignancy	1	0	1

Time to Progression: ITT



Response Rate and CBR

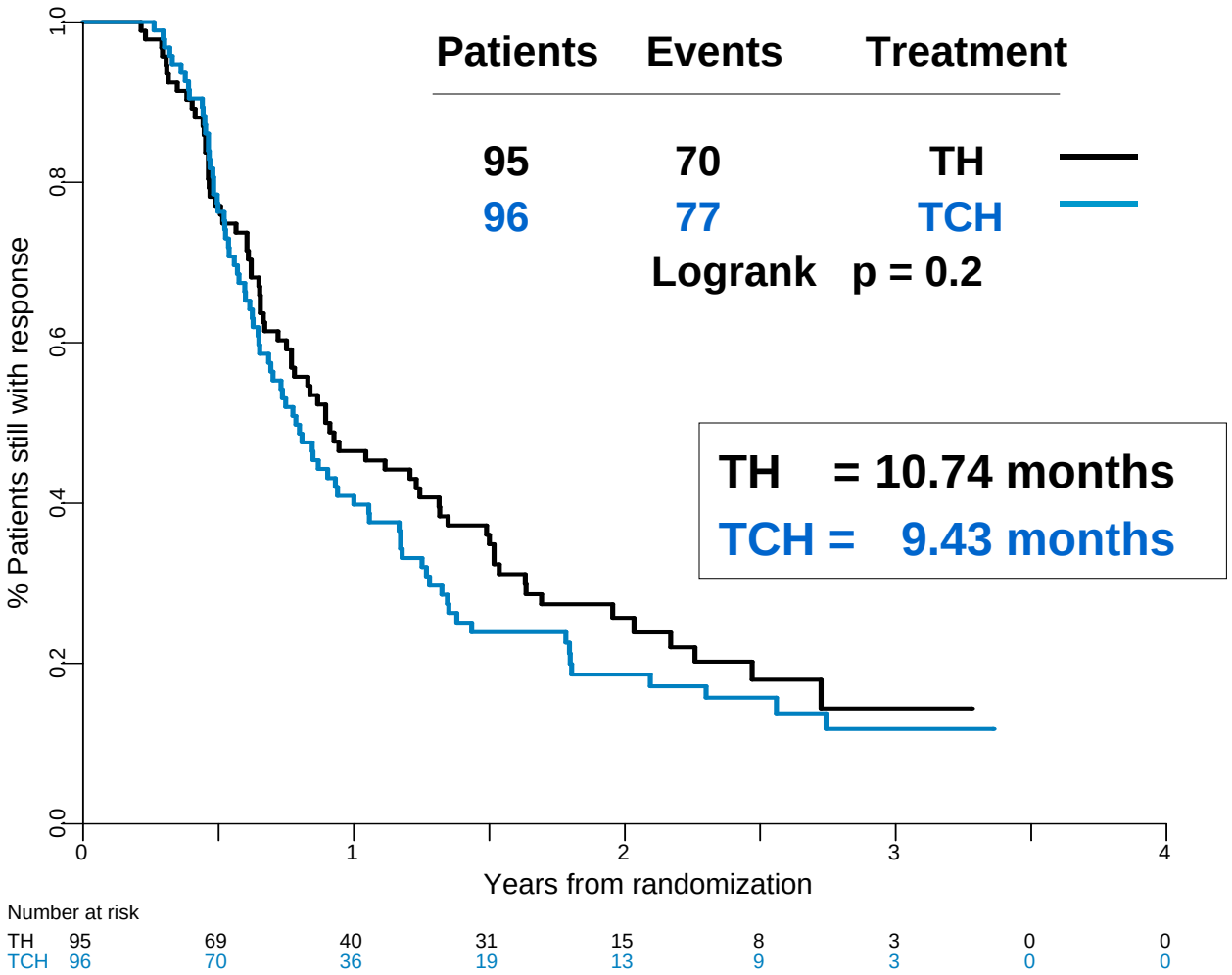
Number of Patients	TH n=131	TCH n=132
Best Overall Response		
CR	24 (18%)	23 (17%)
PR	71 (54%)	73 (55%)
SD/NC	24 (18%)	20 (15%)
PD	11 (8.4%)	11 (8.3%)
NE	1 (0.8%)	5 (3.8%)
RR (CR + PR)	72.5% (64.04-79.95)	72.7% (64.29-80.11)
Clinical Benefit	88 (67%)	88 (67%)
Clinical Benefit Rate	67.2%	66.7%

(CBR: CR, PR or SD for > 24 weeks)

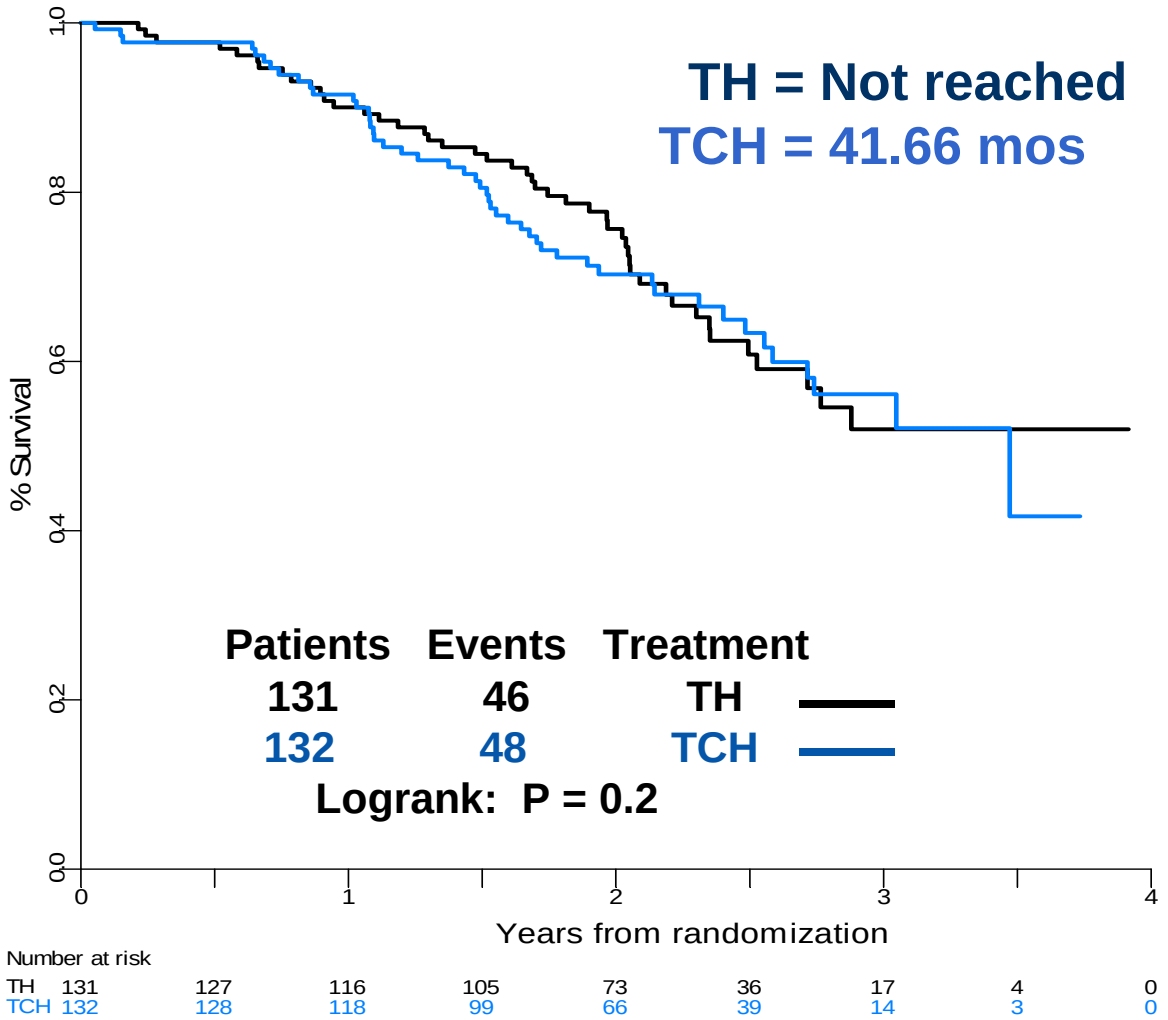
Duration of Response

Number of events	TH n=131	TCH n=132
Total number of patients responding	95	96
Disease Progression	70	77
Median Duration mos	10.74	9.43
95% exact IC	(9.00-15.77)	(7.79-11.99)

Duration of Response: ITT



Overall Survival: ITT



Non-Hematological toxicity

Number	TH 131		TCH 131		P value #
	Overall	**Gr 3 / 4**	**Overall**	**Gr 3 / 4**	
Neuropathy					
Sensory	**75 (57.3%)**	**4 (3.0%)**	**58 (44.3%)**	**1 (0.8%)**	**0.048**
Motor	**12 (9.2%)**	**1 (0.8%)**	**4 (3.1%)**		**0.068**
Arthralgia	**37 (28.2%)**	**1 (0.8%)**	**28 (21.4%)**	**1 (0.8%)**	**0.252**
Myalgia	**58 (44.3%)**	**3 (2.3%)**	**41 (31.3%)**	-	**0.041**
Peripheral edema	**52 (39.7%)**	**5 (3.8%)**	**38 (29%)**	**2 (1.5)**	
Dyspnea	**22 (16.8%)**	**6 (4.6%)**	**18 (13.7%)**	**3 (2.3%)**	
Rash/Desquamat'n	**42 (32.1%)**	**3 (2.3%)**	**20 (15.3%)**	**1 (0.8%)**	**0.002**
Nail changes	**72 (55%)**		**43 (32.8%)**		**<0.001**

Fisher's exact 2 sided P-value

Hematological Toxicity
Grade 3/4

Number of Patients	TH N=131	TCH N=131	P value #
Febrile Neutropenia	16 (12.2%)	17 (13%)	
Infection	38 (29%)	30 (22.9%)	0.324
Neutropenic infection	22 (16.8%)	12 (9.2%)	0.097
Septic death	0	2 (1.5%)	
Anemia	7 (5.3%)	14 (10.7%)	NS
Thrombocytopenia	3 (2.3%)	20 (15.3%)	<0.001

Fisher's exact 2 sided P-value

Related Non-Hematological toxicity

	TH (131)		TCH (131)	
	Overall	Gr 3 / 4	Overall	Gr 3 / 4
Alopecia	126 (96.2%)	NA	127 (96.9%)	NA
Asthenia	105 (80.2%)	7 (5.3%)	103 (78.6%)	16 (12.2%)
Gastrointestinal				
Nausea	70 (53.4%)	-	96 (73.3%)	5 (3.8%)
Vomiting	37 (28.2%)	2 (1.5%)	58 (44.3%)	4 (3%)
Diarrhea	59 (45.0%)	3 (2.3%)	66 (50.4%)	12 (9.2%)
Stomatitis	69 (52.7%)	1 (0.8%)	66 (50.4%)	
Constipation	25 (19.1%)	1 (0.8%)	28 (21.4%)	
Renal failure	1 (0.8%)	-		

Cardiac Toxicity

Number of Patients	TH n=131	TCH n=131
Cardiac Left Ventricular Function		
- Grade 1	6 (4.6%)	6 (4.6%)
- Grade 2	4 (3.5%)	6 (4.6%)
- Grade 3	1 (1.6%)	0
- Grade 4	0	0
Absolute LVEF Decline		
0 -10 points and < LNL	4 (3.1 %)	5 (4.2 %)
11 -15 points and < LNL	3 (2.4 %)	3 (2.5 %)
>15 points and < LNL	7 (5.5 %)	8 (6.7 %)

Conclusions

- Both TH, (T 100), and TCH, (T 75), are effective therapies in this population (TTP > 10 mos)

No significant differences were found for the efficacy endpoints:

TTP, RR, DOR, CBR or OS

Conclusions

- TH and TCH were well tolerated, but had different toxicity 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 major problem with either treatment

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263 women participants

58 independent centers

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