



BCIRG 007 study

First overall survival analysis

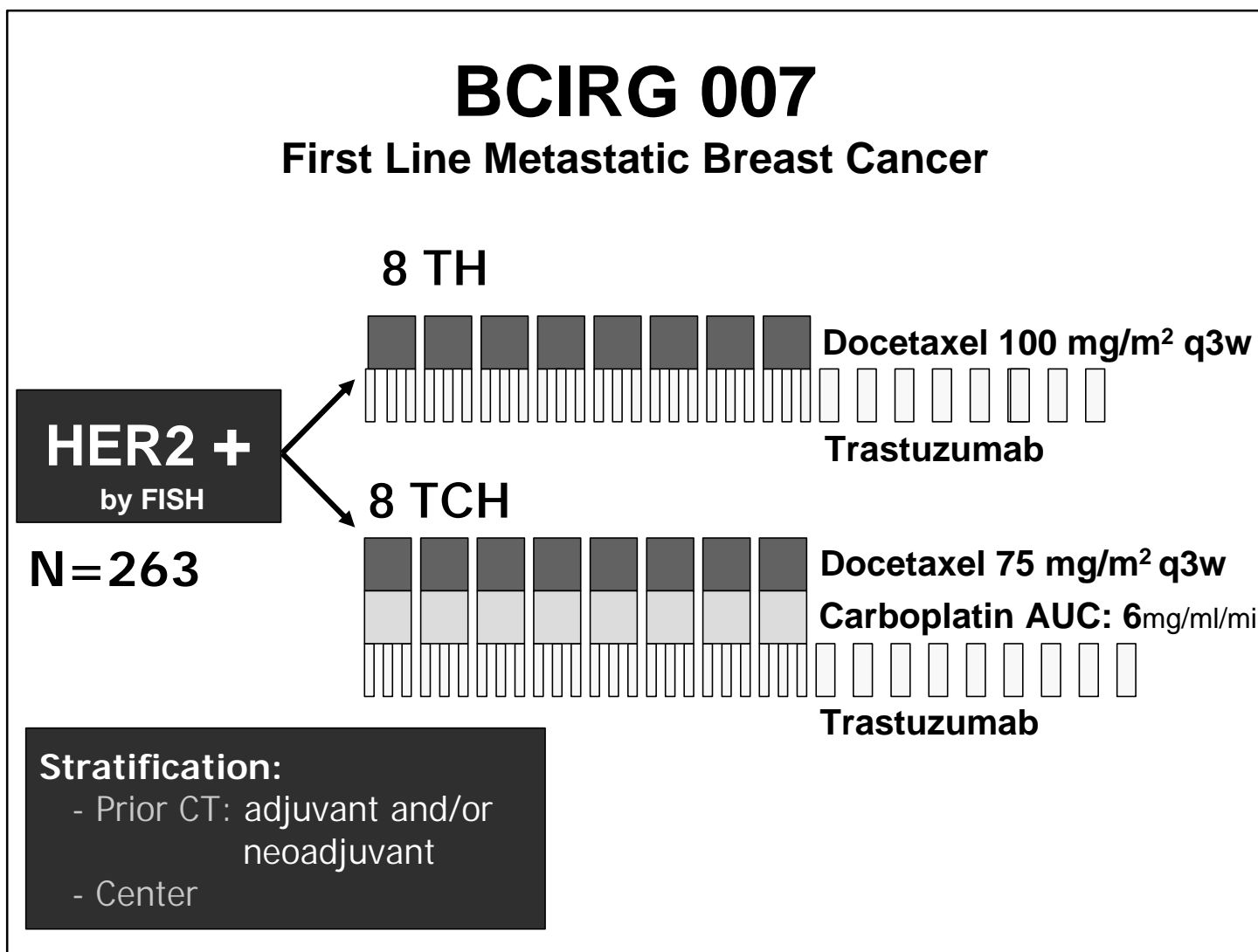
of a multicenter phase III randomized trial comparing docetaxel and trastuzumab with docetaxel, carboplatin and trastuzumab as first line chemotherapy for patients with metastatic breast cancer containing the Her2/neu alteration

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On behalf of the BCIRG 007 Investigators

Rationale for TCH Experimental Arm

- ◆ Synergism between platinum coordination complexes, docetaxel, and trastuzumab
- ◆ High objective overall RR (64% & 77%) and long TTP (12.7 - 17.0 months) in 2 pilot TCH trials in HER2+ MBC
- ◆ Superiority of paclitaxel, carboplatin, trastuzumab compared to paclitaxel, trastuzumab in a randomized trial in HER2+ MBC
- ◆ High path CR rate of TCH in LABC
- ◆ Extensive safety data base of docetaxel + carboplatin combination in clinical trials of ovarian CA and NSCLCA



- ## Statistical Considerations
- ◆ The power of the trial is set to 80%, to detect a 50% improvement in median TTP for patients receiving TCH.
 - ◆ The error rate for a false positive outcome (α) is set to 5%, using two-sided significance tests.
 - ◆ Assuming 5% of patients would be found ineligible, the total sample size needed was 250 (125 patients per treatment arm) in order to achieve a sample of 238 eligible randomized patients.
 - ◆ The analysis of tumor response, TTP and OS was performed on an intent-to-treat basis for all randomized patients.
 - ◆ The Kaplan-Meier product limit method was used to estimate TTP and OS. The logrank test, stratified for prior adjuvant and/or neoadjuvant chemotherapy, was used to compare the two treatment arms.

Patient Characteristics

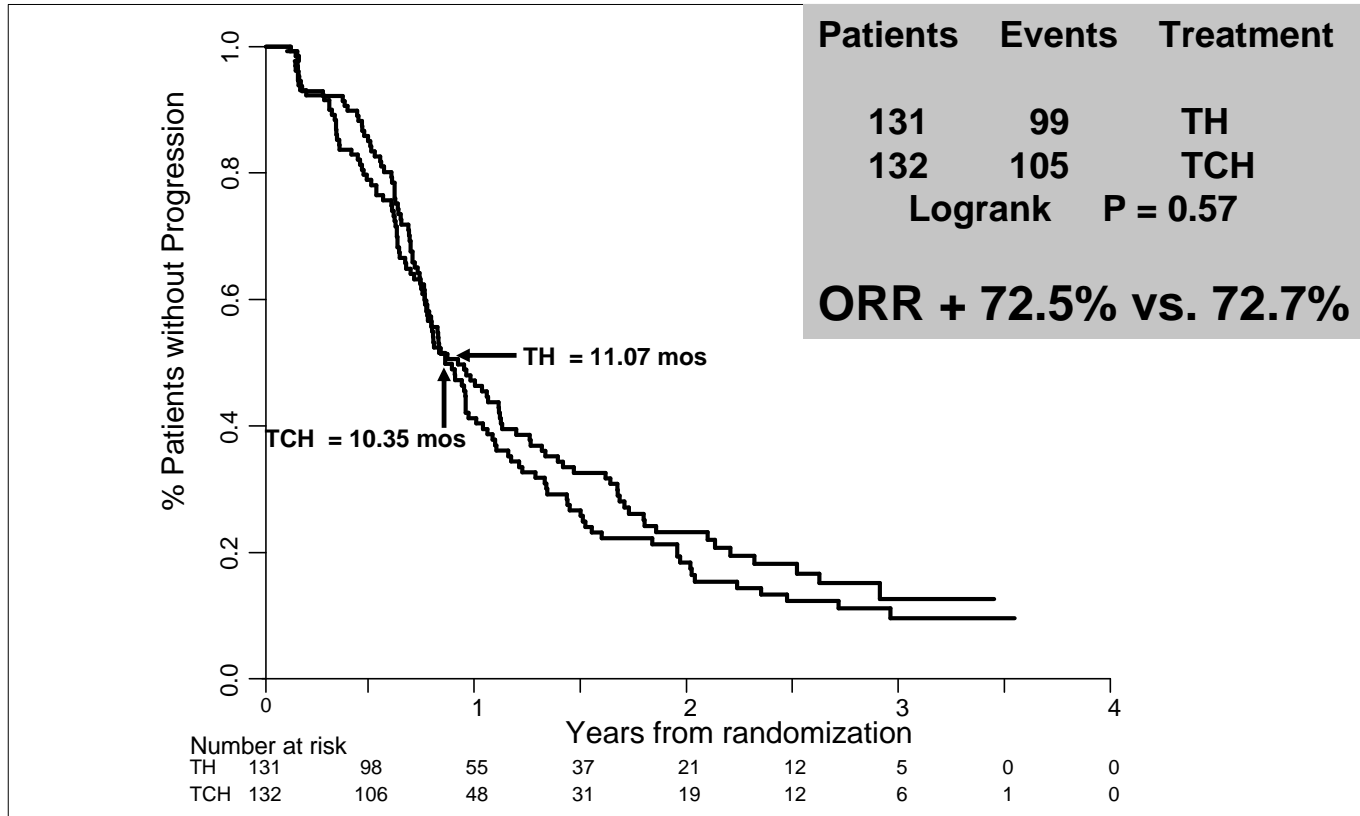
Randomised (n = 263)	TH (n = 131)	TCH (n = 132)
Eligible	125 (95.4%)	128 (97%)
Treated	131 (100%)	131 (99.2%)
Age	52	52
KPS	90	100
Prior Systemic Treatments:		
Endocrine	35 (26.7%)	48 (36.4%)
Chemotherapy (adj):	73 (55.7%)	71 (53.8%)
No prior CT	57 (43.5%)	59 (44.7%)
Prior CT without Tax	60 (45.8%)	61 (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)

ORR & TTP: ITT

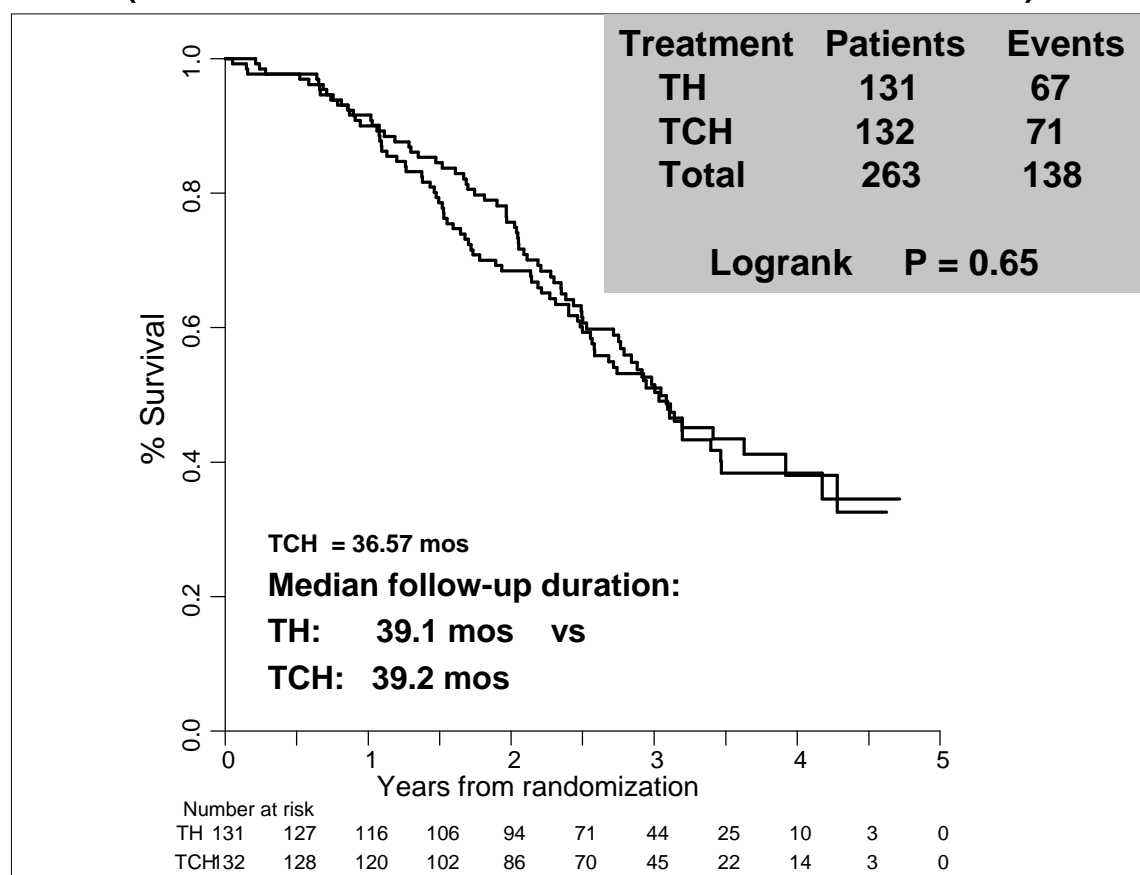
(Dec 26, 2005)



Forbes, et al., ASCO 2006

Main Overall Survival Analysis: ITT

(data cutoff December 26, 2006)



Hematological Toxicity Grade 3/4

Number of Patients	TH N=131	TCH N=131	P value #
Febrile Neutropenia	16 (12.2%)	17 (13.0%)	0.324
Infection	38 (29.0%)	30 (22.9%)	
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

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/Desquamation	42 (32.1%)	3 (2.3%)	20 (15.3%)	1 (0.8%)	0.002
Nail changes	72 (55%)		43 (32.8%)		<0.001
Nausea	70 (53.4%)	-	96 (73.3%)	5(3.8%)	0.0013
Emesis	37 (28.2%)	2(1.5%)	58 (44.3%)	4 (3%)	0.01
LV dysfunction	11 (8.4%)	1 (0.8%)	10 (7.6%)	0 (0%)	

* Fisher's exact 2 sided P-value

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%)* <small>*P=0.29</small>
Relative dose intensity		
Carbo dose intensity relative to cycle 1 dose	-	97.4 %
2 Patients received Cisplatin: Relative Dose intensity: both > 0.9		

Chemotherapy discontinuation

Treated (n=262)	TH n=131	TCH n=131
Discontinued:		
Disease progression	25 (19.1%)	20 (15.2%)
Adverse Events non cardiac	17 (13%)	10 (7.6%)
Adverse Events cardiac	1 (0.8%)	0 (0%)
Consent withdrawn	3 (2.3%)	2 (1.5%)
Death	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%)

Conclusions (I)

- ◆ In contrast to the previous demonstration of superiority of addition of carboplatin to paclitaxel + trastuzumab, the present study failed to demonstrate enhanced efficacy of carboplatin in combination with docetaxel + trastuzumab
- ◆ Though the study was relatively underpowered to detect more modest differences in clinical outcome (e.g. <50% ↑ in TTP), with a median follow-up duration of 39 months, there are no significant differences (TH vs. TCH) in ORR, TTP, or OS
- ◆ Both TH, (T 100), and TCH, (T 75), are effective therapies in this population of HER2-amplified breast cancers (TTP > 10 mos and OS > 36 months)
- ◆ Because of the asymmetry in docetaxel dosing between the two arms, we cannot rule out a contribution of carboplatin in the TCH arm

Conclusions (II)

- ◆ TH was more frequently associated with neuropathy, myalgia, skin/nail changes, and neutropenic infection
- ◆ TCH was associated with more episodes of thrombocytopenia, nausea and emesis
- ◆ There were no significant differences in rates of febrile neutropenia (12.2% vs. 13%; TH vs. TCH, respectively)
- ◆ More patients on TCH received the maximum number of chemotherapy cycles, and numerically fewer patients on TCH discontinued treatment as a result of non-heme toxicity

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58 independent centers	
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