Results of Two Open Label Multicenter Phase II Pilot Studies (BCIRG 101 and 102) with Trastuzumab (Herceptin®) in Combination with Docetaxel and Platinum salts (Cis- or Carboplatin) (TCH) as Therapy for Advanced Breast Cancer in Women Over-Expressing the HER2-neu Proto-Oncogene

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Rationale/Introduction

- **In MBC:**
  - Trastuzumab elicits objective clinical responses in patients with HER2+ MBC
  - Clinical outcomes are improved (including overall survival) with the addition of trastuzumab to chemotherapies such as paclitaxel or anthracyclines
  - Cardiac toxicity may be limiting when Herceptin is used with anthracyclines
  - Docetaxel and platinum salts are active agents in first line MBC
- **In-Vivo and In-Vitro synergy findings**
  - Platinum salts and docetaxel when combined with trastuzumab are extremely synergistic
- **TCH is a novel regimen for incorporation into the adjuvant treatment of HER2 positive, early breast cancer due to the documented synergy and possibility of avoiding the cardiac toxicity of anthracyclines and Herceptin**
- **These studies piloted both platinum salts in TCH prior to utilization in ongoing BCIRG phase III adjuvant and metastatic studies**

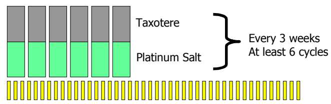
Study Objectives

- **Primary:** Safety; Response rate
- **Secondary:** Duration of Response; Time to Progression; Survival

Enrollment Criteria

- Metastatic breast cancer
- Amplification/Overexpression of HER2 (by immunohistochemistry (Dako 2+ or 3+) or fluorescence in situ hybridization (FISH)
  - (FISH status is retrospectively tested on all patients on primary tumor)
- Stage IIIB or IV
- Prior adjuvant or neo-adjuvant allowed
- Prior chemotherapy for MBC:
  - TCarboH: One allowed
  - TCisH: Not allowed
- Prior treatment with taxanes or platinum salts
  - TCarboH: Monochemotherapy allowed
  - TCisH: Not allowed
- Measurable disease (including lytic bone lesions by MRI)
- ECOG ≤ 2
- Normal baseline LVEF, and hepatic, renal, and bone marrow function within acceptable range

Schema of Administration



Herceptin weekly until PD

Premedication
•Standard Taxotere premed
•Standard CDDP hydration

Treatment Dosage

	BCIRG 101 TCisH	BCIRG 102 TCarboH
Taxotere	75 mg/m²	75 mg/m²
Platinum Salt	Cisplatin 75 mg/m²	Carboplatin 6 AUC
Herceptin	4mg/kg loading 2 mg/kg weekly	4mg/kg loading 2 mg/kg weekly

Treatment Administration (I)

	BCIRG 101 TCisH	BCIRG 102 TCarboH
N	62	62
Chemotherapy Cycles	389	385
Median (Range)	6 (3-8)	6 (2-13)
Herceptin infusions	1937	1956
On CT	1146	1176
Median (range)	18 (7-24)	18 (4-43)
After CT	791	780
Median (range)	13 (1-51)	20 (2-61)

Treatment Administration (II)

		BCIRG 101 TCisH	BCIRG 102 TCarboH
N		62	62
TCH Cycles	≤3	2	6
	4	3	2
	5	4	2
	6	34 (55%)	35 (56%)
	>6	19 (31%)	16 (26%)
TCH Discontinuations		9 (15%)	10 (16%)
	PD	2	6
	Went to Surgery	3	0
	AE	3*	3**
	Pt Withdrawal	1	1

*1 pt with CHF (onset cycle 4, off cycle 5), 2 pts with Gr. 3 neurosensory (cycle 5)
**1 pt with Gr. 3 Diarrhea and edema (cycle 2), 1 pt with cardiac tamponade (cytology positive), 1 pt with pancytopenia and electrolyte imbalance

Patient and Tumor Characteristics

		BCIRG 101 TCisH	BCIRG 102 TCarboH
Number of centers		17	21
Number of Patients		62	62
Median Age (Range)		52 (29-76)	54 (31-76)
ECOG PS	0	40 (65%)	36 (58%)
	1	20 (32%)	25 (40%)
	2	2 (3%)	1 (2%)
Organs involved	1-2	40 (65%)	42 (68%)
	≥ 3 organs	22 (35%)	20 (32%)
Organ involvement			
- Visceral		43 (69%)	43 (70%)
- Liver		24 (39%)	16 (26%)
- Lung		25 (40%)	31 (51%)
- Brain		1 (2%)	3 (5%)
Bone Metastases		29 (47%)	28 (46%)
Bone Lytic only		4 (6%)	5 (8%)

Prior Chemotherapy

	BCIRG 101 TCisH	BCIRG 102 TCarboH
	N=62	N=62
Prior Adjuvant CT	36 (58%)	35 (56%)
Anthracycline CT	20 (32%)	28 (45%)
Prior Adjuvant Taxane	0	9 (15%)
Prior MBC CT	0	3 (5%)

Severe/Gr. 3-4 Hematological Toxicity

	BCIRG 101 TCisH	BCIRG 102 TCarboH
N	62	62
Febrile Neutropenia	8 (13%)	10 (16%)
Infection	2 (3%)	0
Septic death	0	0
Anemia	6 (9%)	4 (6%)
Thrombocytopenia	0	7 (12%)

Non-Hematological Toxicity

	BCIRG 101 TCisH		BCIRG 102 TCarboH	
N	62		62	
	Overall	Gr 3 / 4	Overall	Gr 3 / 4
Alopecia	58 (94%)	NA	43 (69%)	NA
Asthenia	58 (94%)	11 (18%)	50 (81%)	11 (18%)
Gastrointestinal				
Nausea	56 (90%)	11 (18%)	43 (69%)	7 (11%)
Vomiting	43 (69%)	7 (11%)	26 (42%)	5 (8%)
Diarrhea	45 (73%)	7 (11%)	32 (52%)	3 (5%)
Stomatitis	29 (47%)	2 (3%)	31 (50%)	2 (3%)
Constipation	16 (26%)	0	18 (29%)	0
Renal (creatinine)	25 (40%)	2 (3%)	1 (2%)	0
Ototoxicity	23 (37%)	1 (2%)	2 (3%)	0
Neurologic				
Sensory	37 (60%)	2 (3%)	26 (42%)	0
Motor	7 (11%)	1 (2%)	9 (15%)	1 (2%)
Myalgia/arthralgia	18 (29%)	0	14 (23%)	3 (5%)
Peripheral edema	25 (40%)	1 (2%)	20 (32%)	1 (2%)
Skin rash/erythema	17 (27%)	1 (2%)	18 (29%)	1 (2%)
Nail changes	17 (27%)	0	9 (15%)	0

Cardiac Toxicity Monitoring

- Clinical: every cycle
- LVEF (MUGA or ECHO) at:
  - baseline
  - every 12 weeks
  - completion of chemotherapy
  - during Herceptin therapy at any suspected change (TCarboH) or every 3 months in follow-up (TCisH)
- Cardiac toxicity was recorded by NCI Toxicity scale and by LVEF monitoring.

Cardiac Toxicity

	BCIRG 101 TCisH				BCIRG 102 TCarboH			
N	62				62			
NCI Cardiac Term Grade	1	2	3	4	1	2	3	4
Function	15	11	1	0	8	9	1	0
Dysrhythmia	2	2	0	0	0	0	1	0
Absolute LVEF Decrease								
≥ 10 points and < LNL	2				2			
≥ 15 points and < LNL	4				3			
≥ 20 points	4				2			

TCisH - Response Rate

First Line Patients*

All patients were centrally assessed by two independent radiologists

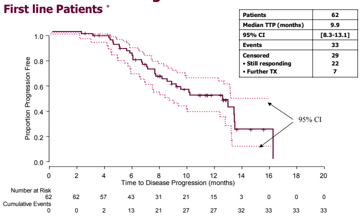
	Overall	FISH positive**	FISH negative**
CR	3	2	1
PR	46	25	15
SD	12	8	2
PD	1	0	1
ORR 95% CI	49/62 (79%) [66-88]	27/35 (77%) [59-90]	16/19 (84%) [60-96]

* All patients are first line
** 8 patients did not have tumor samples available for FISH testing (6 PR and 2 SD)

TCisH – Time to Progression

First line Patients *

Patients	62
Median TTP (months)	9.9
95% CI	[8.3-13.1]
Events	33
Censored	29
• Still responding	22
• Further TX	7

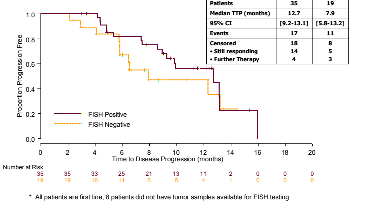


* All patients are first line

TCisH– Time to Progression

First Line Patients by FISH Result*

	FISH +	FISH -
Patients	35	19
Median TTP (months)	12.7	7.9
95% CI	[9.2-13.1]	[5.8-13.2]
Events	17	11
Censored	18	8
• Still responding	14	5
• Further Therapy	4	3



* All patients are first line, 8 patients did not have tumor samples available for FISH testing

TCarboH - Response Rate

First Line Patients*

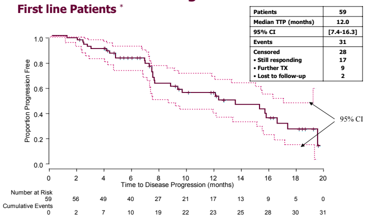
	Overall	FISH positive**	FISH negative**
CR	8	7	1
PR	23	16	6
MR	4	2	1
SD	13	6	7
PD	7	5	2
ORR 95% CI	31/55 (56%) [40-69]	23/36 (64%) [46-79]	7/17 (41%) [19-67]
NE	4	2	2

* 3 patients were treated in second line (1 NC and 2 PD, FISH positive)
** 2 patients did not have tumor samples available for FISH testing (1 PR and 1 MR)

TCarboH – Time to Progression

First line Patients *

Patients	59
Median TTP (months)	12.0
95% CI	[7.4-16.3]
Events	31
Censored	28
• Still responding	17
• Further TX	9
• Lost to follow-up	2



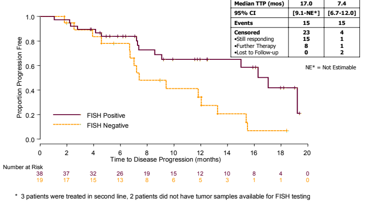
* 3 patients were treated in second line

TCarboH – Time to Progression

First Line Patients by FISH Result*

	FISH +	FISH -
Patients	38	19
Median TTP (mos)	17.0	7.4
95% CI	[9.1-NE*]	[6.7-12.0]
Events	15	15
Censored	23	4
•Still responding	15	1
•Further Therapy	8	1
•Lost to Follow-up	0	2

NE* = Not Estimable



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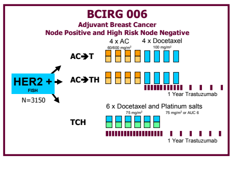
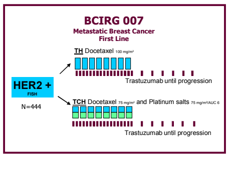
Conclusions

- TCisH and TCarboH in these two separate multicenter phase II trials of HER2 positive MBC patients show the regimens to be:
  - Feasible (6 cycles in almost all patients, 3 pts discontinued due to adverse events in each study)
  - Safe, without any enhancement of the expected toxicity of the individual agents
  - Very active in a population of MBC with poor prognosis
- These pilot studies are the basis of phase III trials in the Adjuvant (BCIRG 006) and Metastatic (BCIRG 007) settings in patients with HER2 positive tumors by FISH