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## ABSTRACT

**Background.** BCIRG 007 is a multicenter, phase III randomized trial comparing docetaxel and trastuzumab [TH] with docetaxel, platinum salt (cisplatin or carboplatin) and trastuzumab (TCH) as first-line chemotherapy in women with metastatic breast cancer (MBC). Women enrolled in the study had to have primary breast tumors with HER2 amplification as determined by centralized FISH analysis.

**Methods.** We determined the percentage of subjects with HER2 amplification who had elevated (> 15 ng/mL) baseline levels of serum HER2 prior to the initiation of trastuzumab-based therapies. Baseline was considered to be the last available determination within 21 days prior to first treatment.

**Results.** The median baseline serum HER2 levels was 75.8 ng/mL (range [8 - 3280 ng/mL]) for all subjects (n = 123), with no statistical difference between subjects randomized to receive TH (median = 65.9 ng/mL, n = 64) and those randomized to receive TCH (median = 89.9 ng/mL, n = 59). Overall, 89% of the 123 subjects with HER2-amplified primary tumors had serum HER2 levels > 15 ng/mL at the time of metastatic disease (86% in TH vs 92% in TCH).

**Conclusions.** There was no statistical impact of baseline serum HER2 levels on any important clinical event: response to treatment, clinical benefit (response or stable disease for more than 24 weeks), disease progression or death. Conversely, when serum HER2 was measured over time, subjects with higher levels had an elevated risk of experiencing progressive disease (p = 0.003), even after adjustment for extent of disease (1 or 2 vs 3 or more organs involved) and presence of visceral disease. These analyses suggest that monitoring serum HER2 levels over the course of disease may be a means for detecting progressive disease in women with HER2 amplified breast cancer. Given the long intervals between the serum HER2 measurement and progression (up to 9 months), caution is required in interpreting these results.

## INTRODUCTION

- Approximately 20% of breast cancer tumors exhibit human epidermal growth factor 2 (HER2) amplification, which is associated with a poor clinical outcome for women with all stages of breast cancer. The extracellular domain (ECD) of the HER2 protein can be cleaved from the surface of breast cancer cells by a metalloprotease producing a soluble protein called HER2 ECD.
- We conducted a multicenter, prospective, non-blinded randomized phase III trial comparing docetaxel and trastuzumab with docetaxel, platinum salts and trastuzumab as first-line chemotherapy for patients with metastatic breast cancer with HER2 gene amplification. A total of 263 patients were included in this study, called BCIRG 007. A substudy assessing the clinical utility of testing serum samples for HER2 ECD was offered to participants in the BCIRG 007 study.

## OBJECTIVES

- To study the relationship between baseline HER2 ECD and the clinical endpoints of the BCIRG 007 study (response to treatment, clinical benefit, time to progression and duration of response).
- To evaluate the relationship between changes in HER2 ECD over time and tumor progression.
- To determine whether HER2 ECD is a predictive factor for the effect of TCH as compared with TH on time to progression and survival.

## MATERIAL & METHODS

- The protocol for the BCIRG 007 substudy required that serum samples for assessment of HER2 ECD be obtained at baseline, at the end of cycle 3, at the end of cycle 6, at the end of chemotherapy, then every 2 months during the first two years of follow-up, as well as at the time of disease progression. The baseline value was the last available HER2 ECD value prior to first administration of drugs, or prior to randomization for non-treated patients.
- Serum HER2 ECD was measured with the ADVIA CENTAUR<sup>®</sup> automated immunoassay system (Siemens Medical Solutions Diagnostics, Tarrytown, NY). This assay is a sandwich immunoassay using two monoclonal antibodies specific for unique epitopes on the extra cellular domain of the HER2 oncoprotein.
- Levels of HER2 ECD  $\geq 15$  ng/mL are considered elevated.

### Statistical methods

- The prognostic impact of HER2 ECD was assessed by considering the following variables:
  - A continuous variable equal to baseline HER2 ECD.
  - A dichotomous variable indicating HER2 ECD < 15 ng/mL vs  $\geq 15$  ng/mL.
  - A 4-class ordered categorical variable (< q<sub>1</sub> vs q<sub>1</sub> - q<sub>2</sub> vs q<sub>2</sub> - q<sub>3</sub> vs > q<sub>3</sub>, where q<sub>i</sub> represents the i<sup>th</sup> quartile of the HER2 ECD distribution).
- The analyses were performed on the following efficacy endpoints:
  - Response (CR or PR as best response to treatment).
  - Clinical benefit (complete or partial response, or stable disease lasting more than 24 weeks).
  - Time to progression (time from randomization to progression, with progression being any breast cancer relapse or death due to breast cancer).
  - Duration of response (time from response to progression).
- The analyses consisted of:
  - Logistic regression to assess the impact of continuous HER2 ECD on dichotomous outcomes (response and clinical benefit).
  - Fisher's exact test to compare proportions of patients with dichotomous outcomes (response and clinical benefit) in different levels of HER2 ECD.
  - Cox proportional hazards regression to assess the impact of HER2 ECD on time-related outcomes (duration of response and time to progression).

### Patient characteristics

- Among the 263 patients included in BCIRG 007 study, a total of 133 patients participated in the substudy; 67 were in the TH treatment arm and 66 in the TCH treatment arm. Baseline values of HER2 ECD were available for 123 patients, 64 randomized to the TH arm and 59 to the TCH arm. There were no statistically significant differences in baseline characteristics.

CHARACTERISTICS	TH (n = 131)	TCH (n = 132)
Age (median years)	52	51
Karnofsky performance status	90 %	100 %
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 treatment, 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 chemotherapy with anthracycline	43 (32.8 %)	43 (32.6 %)

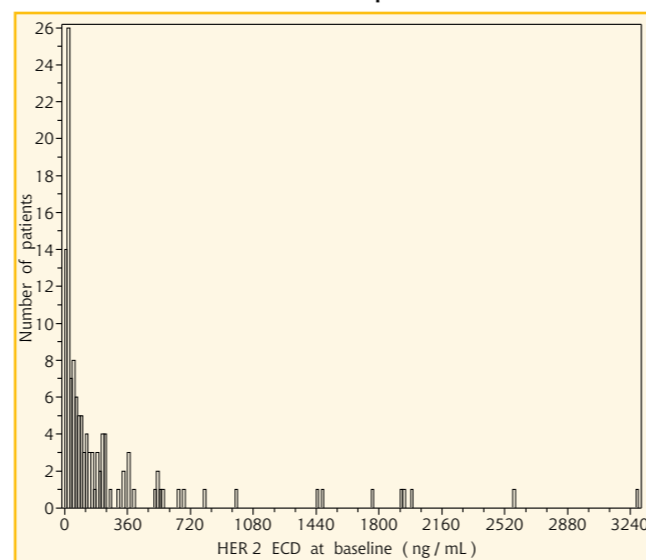
ER = estrogen receptor; PgR = progesterone receptor

### Baseline HER2 ECD levels

- Of the one hundred twenty-three patients, 109 (89%) had HER2 ECD levels > 15 ng/mL at the time of baseline assessment (86% in TH vs 92% in TCH). The median serum HER2 ECD level was 75.8 ng/mL.

	TH (n = 64)	TCH (n = 59)	ALL (n = 123)
HER2 ECD at baseline (ng/mL)			
Median	65.9	89.9	75.8
Range	[8 - 3280]	[10 - 2566]	[8 - 3280]
Category (ng/mL)			
< 15	9 (14 %)	5 (8 %)	14 (11 %)
$\geq 15$	55 (86 %)	54 (92 %)	109 (89 %)

### Baseline HER2 ECD distribution - All patients



## RESULTS

### Impact of baseline HER2 ECD on clinical outcomes

- Baseline HER2 ECD did not have a statistically significant relationship in either treatment arm with best response whether HER2 ECD was dichotomized (p = 1.0), categorized (p = 0.59) or continuous (p = 0.50); nor with clinical benefit, whether HER2 ECD was dichotomized (p = 1.0), categorized (p = 0.73) or continuous (p = 0.20); nor with time to progression, whether HER2 ECD was dichotomized (p = 0.47) or continuous (p = 0.31); nor with duration of response, whether HER2 ECD was dichotomized (p = 0.30) or continuous (p = 0.57).

NUMBER OF Pts WITH HER2 ECD AT BASELINE	< 15 ng/mL (n = 14)	$\geq 15$ ng/mL (n = 109)	ALL (n = 123)
Patient responding			
No	3 (21 %)	24 (22 %)	27 (22 %)
Yes	11 (79 %)	85 (78 %)	96 (78 %)
Patient with clinical benefit			
No	3 (21 %)	27 (25 %)	30 (24 %)
Yes	11 (79 %)	82 (75 %)	93 (76 %)

### Repeated HER2 ECD measurements over time

- A total of 766 HER2 ECD measurements were taken over time in the 133 patients of the substudy. About half of the patients included in the substudy were still at risk at the 18<sup>th</sup> follow-up visit after baseline. Of the patients at risk, 92% had a HER2 ECD value at baseline, between 61% and 64% during chemotherapy, and between 59% and 66% for the first four follow-up visits. Less than half of the patients at risk had a HER2 ECD value at the fifth follow-up visit, with the proportion dropping continuously until the 18<sup>th</sup> follow-up visit.
- The average time between the last HER2 ECD value and progression (or censoring for patients who did not progress) was 57 days.

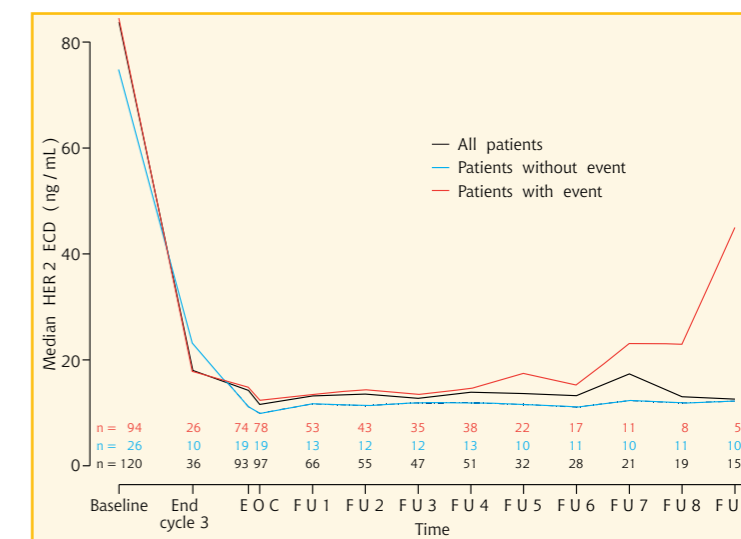
TOTAL NUMBER OF Pts WITH HER2 ECD ASSESSMENTS	TH (n = 67)	TCH (n = 66)	ALL (n = 133)
Number of days between last HER2 ECD assessment and progression* Median and [Range]	55.0	59.5	57.0
	[0 - 1071]	[0 - 1225]	[0 - 1225]

\* Taking into account assessment done at progression, death due to breast cancer and censoring date

### Impact of repeated HER2 ECD measurements on time to progression

- The median HER2 ECD over time showed an initial drop of HER2 ECD after initiation of treatment, and then remained relatively stable over time (see graph below). When the median was calculated separately for patients with an event (progression or death) and for patients without an event, there was a trend for the median HER2 ECD to increase over time for patients with an event compared with patients without an event.

### Median HER2 ECD evolution over time



- When serial measurements of HER2 ECD levels were considered, subjects with higher HER2 ECD levels had an elevated risk of experiencing progressive disease (p = 0.003), even after adjustment for extent of disease (1 or 2 vs 3 or more organs involved) and presence of visceral disease. An increase of 15% in successive HER2 ECD measurements had a high positive predictive value (83%) but a poor negative predictive value (27%) for tumor progression. There was no interaction between the effect of successive HER2 ECD measurements and treatment, suggesting that HER2 ECD is not a predictive factor for the effect of TCH as compared with TH on time to progression.

## CONCLUSION

- In summary, the BCIRG 007 HER2 ECD substudy demonstrated that:
  - Approximately 90% of the subjects with HER2-amplified metastatic breast cancer had elevated HER2 ECD levels (> 15 ng/mL) at the time of study entry.
  - The baseline HER2 ECD did not have a statistically significant relationship with response, clinical benefit, duration of response or time to progression.
  - Positive predictive value of the measurement was good: when serial measurements of HER2 ECD were considered, 83% of the patients with a 15% relative increase in HER2 ECD had a tumor progression within up to 9 months after the last measurement of ECD.
  - In contrast, negative predictive value was low: only 27% of cases without an increase in HER2 ECD levels remained free of progression.
  - HER2 ECD levels were not measured as regularly as specified in the protocol, therefore we suggest caution in interpreting the results of the study.

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