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BCIRG 007 : Serum HER 2 levels in women with metastatic HER 2 - amplified Breast Cancer

V Valero[1], H Roche[2], T Pienkowski[3], J Canon[4], Y Zhao[5], W Carney[6], J Mackey[7], H Taupin[8], M Buyse[9], D Slamon[5]

[1] M D Anderson Cancer Center, Houston, T X (U S A) ; [2] Institut Claudius Regaud, Toulouse (FRANCE) ; [3] M S Curie Memorial Cancer Centre, Warsaw (POLAND) ; [4] C H Notre - Dame, Charleroi (BELGIUM) ; [5] UCLA, Los Angeles, CA (USA); [6] Siemens Medical Solutions Diagnostics, Tarrytown, NY (USA); [7] Cross Cancer Institute, Edmonton, AB (CANADA); [8] CIRG, Paris (FRANCE); [9] IDDI, Louvain-la-Neuve (BELGIUM)

ABSTRACT

Background. BCIRG 007 is a multicenter, phase III randomized trial comparing docetaxel and trastuzumab [T H] with docetaxel, platinum salt (cisplatin or carboplatin) and trastuzumab (T C H) as first - line chemotherapy in women with metastatic breast cancer (M B C). Women enrolled in the study had to have primary breast tumors with HER 2 amplification as determined by centralized F I S H analysis.

Methods. We determined the percentage of subjects with HER 2 amplification who had elevated (> 15 ng / mL) baseline levels of serum HER 2 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 H E R 2 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 T H (median = 65.9 ng / mL, n = 64) and those randomized to receive T C H (median = 89.9 ng / mL, n = 59). Overall, 89 % of the 123 subjects with HER 2 - amplified primary tumors had serum HER 2 levels > 15 ng / mL at the time of metastatic disease (86 % in T H vs 92 % in T C H).

Conclusions. There was no statistical impact of baseline serum H E R 2 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 H E R 2 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 H E R 2 levels over the course of disease may be a means for detecting progressive disease in women with H E R 2 amplified breast cancer. Given the long intervals between the serum H E R 2 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 (HER 2) amplification, which is associated with a poor clinical outcome for women with all stages of breast cancer. The extracellular domain (E C D) of the H E R 2 protein can be cleaved from the surface of breast cancer cells by a metalloprotease producing a soluble protein called H E R 2 E C D.
- We conducted a multicenter, prospective, non - blinded randomized phase I I I trial comparing docetaxel and trastuzumab with docetaxel, platinum salts and trastuzumab as first - line chemotherapy for patients with metastatic breast cancer with HER 2 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 HER 2 ECD was offered to participants in the BCIRG 007 study.

OBJECTIVES

- To study the relationship between baseline HER 2 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 H E R 2 E C D over time and tumor progression.
- To determine whether H E R 2 E C D is a predictive factor for the effect of T C H as compared with T H on time to progression and survival.

MATERIAL & METHODS

- The protocol for the B C I R G 007 substudy required that serum samples for assessment of H E R 2 E C D 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 H E R 2 E C D value prior to first administration of drugs, or prior to randomization for non - treated patients.
- Serum H E R 2 E C D was measured with the A D V I A CENTAUR® automated immunoassay system (Siemens Medical Solutions Diagnostics, Tarrytown, N Y). This assay is a sandwich immunoassay using two monoclonal antibodies specific for unique epitopes on the extra cellular domain of the H E R 2 oncoprotein.
- Levels of H E R 2 E C D ≥ 15 ng / mL are considered elevated.

Statistical methods

- The prognostic impact of H E R 2 E C D was assessed by considering the following variables :
  - A continuous variable equal to baseline H E R 2 E C D.
  - A dichotomous variable indicating HER 2 ECD < 15 ng / mL vs ≥ 15 ng / mL.
  - A 4 - class ordered categorical variable (< q_1 vs q_1 – q_2 vs q_2 – q_3 vs > q_3, where q_i represents the i^{th} quartile of the H E R 2 E C D distribution).
- The analyses were performed on the following efficacy endpoints :
  - Response (C R or P R 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 HER 2 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 H E R 2 E C D,
  - Cox proportional hazards regression to assess the impact of HER 2 ECD on time - related outcomes (duration of response and time to progression).

RESULTS

Patient characteristics

- Among the 263 patients included in BCIRG 007 study, a total of 133 patients participated in the substudy ; 67 were in the T H treatment arm and 66 in the T C H treatment arm. Baseline values of HER 2 ECD were available for 123 patients, 64 randomized to the T H arm and 59 to the T C H arm. There were no statistically significant differences in baseline characteristics.

CHARACTERISTICS		T H (n = 131)	T C H (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 %)

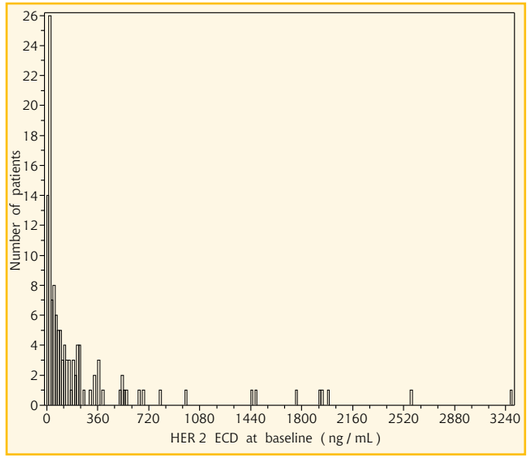
E R = estrogen receptor ; PgR = progesterone receptor

Baseline HER 2 ECD levels

- Of the one hundred twenty - three patients, 109 (89 %) had H E R 2 E C D levels > 15 ng / mL at the time of baseline assessment (86 % in T H vs 92 % in T C H). The median serum H E R 2 E C D level was 75.8 ng / mL.

		T H (n = 64)	T C H (n = 59)	ALL (n = 123)
HER 2 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 %)
	≥ 15	55 (86 %)	54 (92 %)	109 (89 %)

Baseline HER 2 ECD distribution - All patients



Impact of baseline HER 2 ECD on clinical outcomes

- Baseline HER 2 ECD did not have a statistically significant relationship in either treatment arm with best response whether HER 2 ECD was dichotomized (p = 1.0), categorized (p = 0.59) or continuous (p = 0.50) ; nor with clinical benefit, whether HER 2 ECD was dichotomized (p = 1.0), categorized (p = 0.73) or continuous (p = 0.20) ; nor with time to progression, whether HER 2 ECD was dichotomized (p = 0.47) or continuous (p = 0.31) ; nor with duration of response, whether HER 2 ECD was dichotomized (p = 0.30) or continuous (p = 0.57).

NUMBER OF Pts WITH HER 2 ECD AT BASELINE		< 15 ng / mL (n = 14)	≥ 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 HER 2 ECD measurements over time

- A total of 766 HER 2 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 18th follow - up visit after baseline. Of the patients at risk, 92 % had a H E R 2 E C D 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 HER 2 ECD value at the fifth follow - up visit, with the proportion dropping continuously until the 18th follow - up visit.
- The average time between the last HER 2 ECD value and progression (or censoring for patients who did not progress) was 57 days.

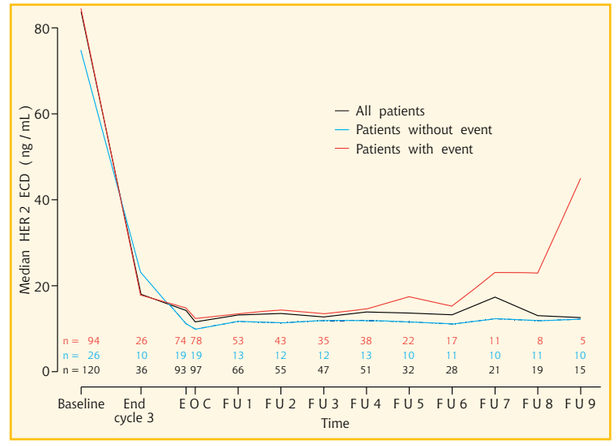
TOTAL NUMBER OF Pts WITH HER 2 ECD ASSESSMENTS	T H (n = 67)	T C H (n = 66)	ALL (n = 133)
Number of days between last HER 2 ECD assessment and progression * Median and [Range]	55.0 [0 - 1071]	59.5 [0 - 1225]	57.0 [0 - 1225]

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

Impact of repeated HER 2 ECD measurements on time to progression

- The median H E R 2 E C D over time showed an initial drop of H E R 2 E C D 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 H E R 2 E C D to increase over time for patients with an event compared with patients without an event.

Median HER 2 ECD evolution over time



- When serial measurements of HER 2 ECD levels were considered, subjects with higher HER 2 ECD levels had an elevated risk of experiencing progfressive disease (p = 0.003), even after adjustement for extent of disease (1 or 2 vs 3 or more organs involved) and presence of visceral disease. An increase of 15 % in successive HER 2 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 HER 2 ECD measurements and treatment, suggesting that HER 2 ECD is not a predictive factor for the effect of T C H as compared with T H on time to progression.

CONCLUSION

- **In summary, the BCIRG 007 HER 2 ECD substudy demonstrated that :**
  - **Approximately 90 % of the subjects with HER 2 - amplified metastatic breast cancer had elevated HER 2 ECD levels (> 15 ng / mL) at the time of study entry.**
  - **The baseline HER 2 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 HER 2 E C D were considered, 83 % of the patients with a 15 % relative increase in HER 2 ECD had a tumor progression within up to 9 months after the last measurement of E C D.**
  - **In contrast, negative predictive value was low : only 27 % of cases without an increase in HER 2 ECD levels remained free of progression.**
  - **HER 2 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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