SABCS 2003

# 318

# Serial Monitoring of Serum HER-2 Extra-Cellular Domain during Herceptin®-Taxol® or Herceptin® alone Therapy for Metastatic Breast Cancer Patients: Preliminary Results from the French Experience (HER.ME.S protocol).


**Gligorov J.[1], Brault D.[1], Tsé C.[1], Lelay K.[2], Antoine M.[1], Campone M.[3], Kerbrat P.[4], Lortholary A.[5], Delozier T.[6], Provent S.[1], Brindel I.[7], Lega E.[1], Hocini H.[8], Maindrault-Goebel F.[9], Simon J-M.[10], Lehmann B.[11], Bernard M.[1], Launois R.[2], Lotz J-P[1].**

***1-CancerEst, AP-HP, Hôpital Tenon, Paris; 2- REES, Paris; 3- Centre René Gauducheau, Nantes; 4-Centre E. Marquis, Rennes; 5- Centre P. Papin, Angers ; 6- Centre F. Baclesse, Caen, 7- DRRC, AP-HP, Paris ; 8- Hôpital St-Louis; 9- Hôpital St Antoine; 10- Hôpital Pitié-Salpétrière ; 11- AGEPS, AP-HP, Paris - France .***


## Rationale

HER2 over expression is a prognostic factor. It is also the target of trastuzumab (anti HER2 monoclonal antibody immunotherapy). In approximately 60% of Metastatic Breast Cancer (MBC) patients with HER2 over-expressed tumours, the HER2 extra cellular domain (H-ECD), undergoes proteolytic cleavage from the full-length protein and is shed as a circulating "antigen". H-ECD could be detected by enzyme immunoassays.
Trastuzumab therapy had to be probably early initiated in MBC patients over expressing HER2. Different protocols are possible (trastuzumab alone or with chemotherapy). Two modalities of trastuzumab treatment are possible in France: monotherapy for patients pre-treated with anthracyclines and taxanes; or associated with paclitaxel for patients pre-treated by anthracyclines.
French ministry of health, searching to evaluate the economical impact of trastuzumab treatment in MBC has mandated a multicentric group for answering this question.

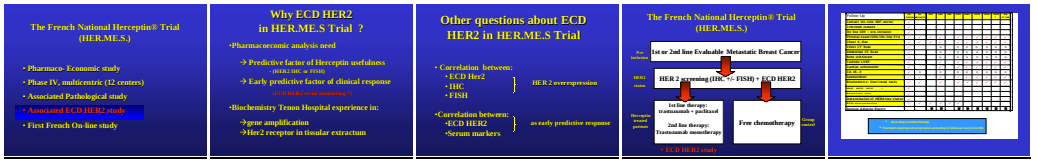
H-ECD has been also reported to be a treatment efficacy independent predictor, but essentially regarding the initial level at MBC. The serum H-ECD kinetic, (level ratio before treatment/after one cycle) is not used routinely as an early predictor of trastuzumab and/or chemo sensitivity.
In this prospective trial we try to evaluate the potential impact of serum H-ECD kinetic on clinical monitoring of HER2+ MBC receiving trastuzumab therapy.

## Material and Methods

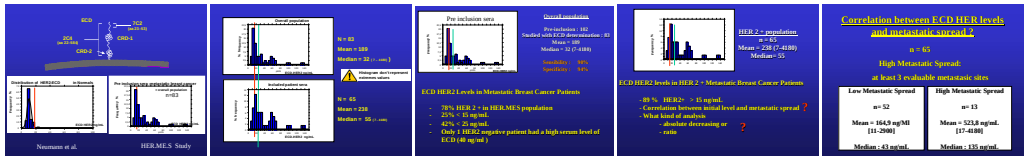
French protocol HER.ME.S is a phase IV multicentric study, evaluating the pharmaco-economic aspect of trastuzumab treatment on MBC with HER2 overexpressing tumours. We were also interested to determine whether serum levels of H-ECD would predict the course of disease in HER-2+ MBC patients. Patients in first or second line MBC untreated with trastuzumab were first pre-ncluded to determine HER2 status. Only HER2 positive patients were finally included. Trastuzumab was delivered weekly (2mg/kg) or three weekly (6mg/kg) associated or not with paclitaxel (175 mg/m² three weekly or 80 mg/m² weekly). Treatments were delivered until progression or unacceptable toxicity.
HER2 tumour status was determined using Immuno-histochemistry methods (3+) or FISH (+, > 2 genes copies per nucleus). H-ECD status was determined using a centralised elisa technique (Oncogene Science-Bayer Diagnostics® - Elisa kit). The H-ECD levels were determined during the following periods: pre-inclusion, inclusion (day 0), then days 28, 56, 84, 102 and 120 for HER-2+ patients.
Evaluation of the disease was performed according to the RECIST criteria every 2 months until withdrawn of the study.
Left ventricular ejection function (LVEF) was monitored every two month using echo cardiograph, and trastuzumab treatment was suspended if LVEF decrease more than 20% comparing before treatment (even if LVEF was > 50%) or LVEF < 50%.

In a two-year period, 83 patients have been screened for HER-2 status (pre-included). Sixty five of them were considered HER2+.

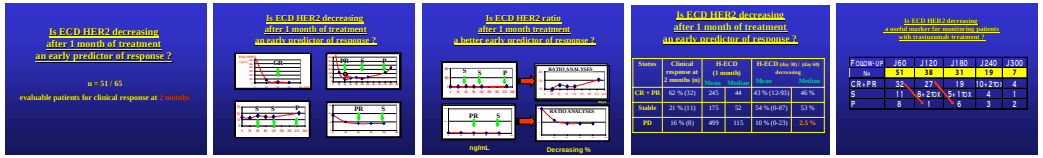
## Results




Regarding the long term indication of trastuzumab in HER2+ MBC patients, the development of new chemotherapeutic associations with this agent and the cost of a long term targeted therapy, the HER.MES group try to identify early predictors of therapeutic efficacy. H-ECD appears regarding literature to be a good candidate and the potential impact of H-ECD level monitoring was prospectively studied. In a two-year period, 83 patients have been screened for HER-2 status (pre-included). Sixty-five of them were HER-2+ (IHC or FISH). Mean age was 53,6 years. Eighty percent of the patients received adjuvant chemotherapy treatment. H-ECD level was 238 ng/ml (median) in HER2 over expressed population (n=65).




Considering patients who could be pre-included in the study if the HER2 status was not known, all MBC patients didn't have tumours with HER2 over expression. Nevertheless using Wilcoxon-test there was a correlation (p< 0,0001) between HER-2 over expressing (FISH and/or IHC) and H-ECD levels (upper limit of normal < 15ng/ml ). Looking the metastatic spread of the disease, H-ECD levels seems to be strongly correlated with the number of metastatic sites (p< 0,0364, Wilcoxon test). These results seem equal to those previously published (1-3). H-ECD could be an important parameter for early diagnosis and spread of metastatic disease in patients with HER2 over expressed tumours.




After two months of treatment 59 patients were evaluable for radiological response, and 51 for kinetic profiling of H-ECD level. The median duration of treatment was 7 months. Twenty-one patients had progressed and 10 had toxicity (4 cardiac toxicities = 6,8%). Regarding the results, H-ECD level at 1 month was never decreasing for progressive patient, was poorly decreasing for patients with stable disease (mean decreasing level 10% [ 41%; -135%]) and significantly decreasing for responders (mean decreasing level 44% [6%; 89%]). There is a strong statistical correlation between the H-ECD kinetic (H-ECD day 30 / baseline) and the radiological response evaluated after 2 months of treatment (p< 0,0001, Wilcoxon test). Relative risk of radiological progression is 10 if H-ECD increases at day 30 comparing to the baseline (before treatment), and relative risk of radiological response is 24 if H-ECD decreases at day 30 comparing to the baseline. There was no correlation between the H-ECD levels at day 60, 120 and 240 and the radiological response but the follow-up was too short for the majority of the patients ongoing the trial.

## Conclusions and discussion

Trastuzumab is an essential treatment for patients with HER-2 over expressing tumours with an impact on overall survival (4). Recently was demonstrated that early administration of trastuzumab could favourably impact overall survival of these population (5).
However preliminary results suggest efficiency of different protocols associating trastuzumab and chemotherapy. For clinicians, the usefulness of a new marker in HER2 population could be of great interest helping strategies decisions in this population of patients.

Regarding the preliminary results of HER.ME.S trial, H-ECD level seems very interesting because of:

- High sensitivity and specificity
- Targeting for therapy
- Prognosis
- Early prediction of treatment response

Some informations are needed to specify the place of H-ECD routinely.
Does decrease of ECD predict TTP better than other parameters?
It doesn't seem that the monitoring of follow-up and therapy effects could be definitely done just by H-ECD levels.
The economical impact of H-ECD monitoring is ongoing and final analyses will be presented when the patients follow-up will be relevant.

## Bibliography


1. Cook GB et al. Anticancer Res 2001; 21: 1465-70.
2. Molina R et al. Anticancer Res 1999; 19: 2551-5.
3. Molina R et al. Br J Cancer 1996; 74: 1126-31.
4. Slamon DJ et al. N Engl J Med. 2001; 344: 783-92.
5. Extra JM et al. Eur J Cancer 2003; 29: S202.