FINAL RESULTS FROM TRASTYVERE STUDY: A RETROSPECTIVE ANALYSIS OF HEAVILY PRETREATED HER2-POSITIVE METASTATIC BREAST CANCER (MBC) PATIENTS TREATED IN SPAIN WITH LAPATINIB PLUS TRASTUZUMAB AS COMPASSIVE THERAPY

Authors:

J. Gávila[1], B. Bermejo[2], L. Manso[3], E. Muñoz[4], A. Antón[5], J. Brunet[6], C.A. Rodríguez[7], A. Santaballa[8], J. Cortés[4,10], A. Llombart[9,10].

[1]Instituto Valenciano de Oncología, Oncology, Valencia, Spain. [2]Hospital Clínico Universitario de Valencia, Oncology, Valencia, Spain. [3]Hospital 12 de Octubre, Oncology, Madrid, Spain. [4]Vall d' Hebron Institute of Oncology (VHIO), Oncology, Barcelona, Spain. [5]Hospital Universitario Miguel Servet, Oncology, Zaragoza, Spain. [6]Institut Català d' Oncologia Girona, Oncology, Girona, Spain. [7]Hospital Universitario de Salamanca-IBSAL, Oncology, Salamanca, Spain. [8]Hospital Universitario la Fe de Valencia, Oncology, Valencia, Spain. [9]Hospital Arnau de Vilanova de Valencia, Oncology, Valencia, Spain [10]Medica Scientia Innovation Research (MedSIR ARO), Barcelona, Spain.

BACKGROUND

- Vertical dual blockade with lapatinib (L) and trastuzumab (T) in heavily pretreated HER2-positive MBC patients has shown consistent activity in a phase III trial, yielding to an EMA approval for the hormone-negative subgroup [1,2].
- However, the study was conducted among lapatinib naïve patients and there is no information about the futility of the combination in clinical practice.
- The study hypothesis is that dual blockade, in patients previously exposed to antiHER2 agent, is able to provide a clinical benefit rate (CBR) similar to the Blackwell study results (25%) [1].

MATERIAL AND METHODS

- We conducted a retrospective analysis among patients treated in Spain by compassive therapy for the combination of L-T.
- The study was approved by the regulatory authorities and Ethics committees from all participating centers. A signed consent form was required for surviving patients.
- **Major inclusion criteria were**
  - HER2[+] metastatic or locally advanced MBC;
  - ECOG status 0 – 2;
  - Progression on at least one prior line of trastuzumab for advanced disease;
  - L-T treatment started before JAN/2013. Concomitant endocrine therapy for hormone-positive patients as well as patients with brain metastasis and/or prior exposure to L was allowed.
  - Chemotherapy combinations were excluded.
- **Primary Outcome**
  - Clinical Benefit Rate (CBR) defined as the percentage of patients that achieved and objective response (CR or PR) or tumor stabilization for at least 24 weeks during the period of treatment with the LT combination. Clinical response rate will be assessed by RECIST criteria v 1.1.
- **Secondary Outcomes**
  - Time to progression (TTP)
  - Overall survival (OS)
  - Toxicity
- **Sample size**
  - A total of 111 patients were predefined for the primary outcome.
  - A total of 123 patients from 13 institutions were eligible. Finally 115 (94%) patients were included. The reason of patient exclusion was missing information in clinical history.
  - **The information of 115 patients was completed and independently monitored.**

RESULTS

- **Baseline description serie:**
  - The median age of the series was 59.8 years (34 – 84); 63.5% hormone-positive; 77.4% visceral disease; 33% CNS disease; 47.8% with 3 or more organs involved. Median number of prior T lines 3 (Interquartile Range (IQR) 2-5); 63.5% previously treated with L (Table 1).
  - All patients were treated with antiHER2 agent (trastuzumab (58.3%) or lapatinib (41.7%)) in prior line and after dual blockade line (trastuzumab (83.8%) and/or lapatinib (29.4%)). No patients in prior line were treated with L plus T combination.
- **Effectiveness analysis:**
  - A total of **40 patients (34.8%)** achieved a **CBR** (95%CI 26.1– 43.5%): 6 CR, 19 PR and 15 and 15 stable disease > 24 weeks (Table 2). The Overall Response Rate **(ORR) was 21.7%** (95%CI 14.2 – 29.3%).
  - The median time to progression **(TTP) was 3.9 months** (95%CI 3.25 – 5.1) and the median overall survival **(OS) was 21.6 months** (95%CI 17.1 – 27.2) (Figure 1-2).
- **Subgroups analysis:**
  - **Previous L treatment and hormonal receptor (HR) status did not condition CBR, TTP and OS** (Table 3 and Figures 3-6).
  - Higher TTP (p=0.058, significant trend) was observed in patients with <3 vs. ≥3 previous T lines (Figure 7).
  - **Lower CBR, median TTP and OS** were observed in patients with **central nervous system (CNS) metastases** than those with no evidence of the disease. However only differences in OS were statistically significant (Table 3 & Figure 8-9).
- **Toxicity:**
  - Lapatinib plus trastuzumab treatment-related toxicities were reported in 63 patients (54.8%). Severe toxicities were reported in 19 patients (16.5%). The most frequent toxicity was gastrointestinal disorders.
  - **Severe non hematological and hematological toxicities** were reported in **19 (16.5%) and 2 patients (1.7%),** respectively. **Only 2 patients report cardiac toxicities.**

Table 1. Baseline description series

Parameters	Total Sample (n=115)	No previous L (n=42)	Previous L (n=73)	p- value
Median age (years), median (range)	59.8 (34 to 84)	61.5 (34 to 89)	59 (39 to 81)	0.38
Total number of prior lines, median (IQR)				
Trastuzumab	3 (2 to 5)	3 (2 to 4)	4 (2 to 5)	0.061
Lapatinib	1 (0 to 1)	0 (0 to 0)	1 (1 to 1)	NA
MBC previous lines, median (IQR)				
Trastuzumab	3 (2 to 4)	2 (2 to 4)	3 (2 to 5)	0.18
Lapatinib	1 (0 to 1)	0 (0 to 0)	1 (1 to 1)	NA
ECOG, n (%)				
0	30 (26.1)	14 (33.3)	16 (21.9)	0.179
>=1	85 (73.9)	28 (66.7)	57 (78.1)	
Hormonal receptor (HR), n (%)				
ER or PR (+)	73 (63.5)	28 (66.7)	45 (61.6)	0.59
Metastatic sites, n (%)				
Central nervous system	38 (33)	12 (28.6)	26 (35.6)	0.439
Hepatic	54 (47)	17 (40.5)	37 (50.7)	0.291
Lung	56 (48.1)	15 (34.3)	41 (54.9)	0.035
Visceral disease	89 (77.4)	26 (61.9)	63 (86.3)	0.003
Number of organs involved, n (%)				
<3	60 (52.2)	22 (52.4)	38 (52.1)	0.973
>=3	55 (47.8)	20 (47.6)	35 (47.9)	

Table 2. Primary objetive analysis

Parameters	Total Sample (n=115)
Clinical Benefit Rate (CBR), n(%) (95%CI)	40 (34.8) [26.1 to 43.5]
Complete Response, n(%)	6 (5.2)
Partial Response, n(%)	19 (16.5)
Stable Disease, n(%)	15 (13)

Table 3. Subgroup analysis

Parameters	CBR, n (%)	RR 95%CI, p-value
Previous Lapatinib		1.3 [0.8 to 2.1], p=0.331
Yes (n=73)	23 (31.5)	
No (n=42)	17 (40.5)	
Previous Lines with T		1.2 [0.7 to 2], p=0.447
>=3 (74)	24 (32.4)	
<3 (n=41)	16 (39)	
Estrogen receptor		0.9 [0.5 to 1.4], p=0.572
+ (n=66)	20 (30.3)	
- (n=49)	20 (40.8)	
Central Nervous System Metastases (CNSm)		1.2 [0.7 to 2], p = 0.612
With CNSm (n=38)	12 (31.6)	
Without CNSm (n=77)	28 (36.4)	

Figure 1. Time to progression for total population of the study

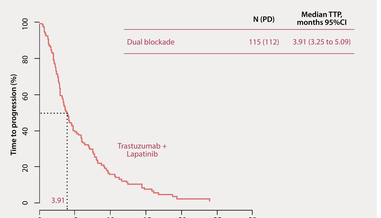


Figure 2. Overall survival for total population of the study

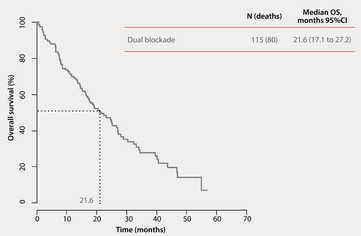


Figure 3. Time to progression according previous lapatinib treatment

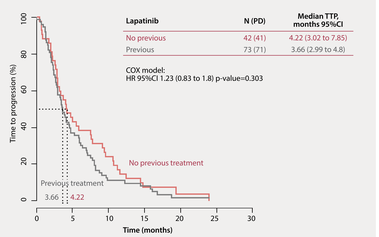


Figure 4. Overall survival according previous lapatinib treatment

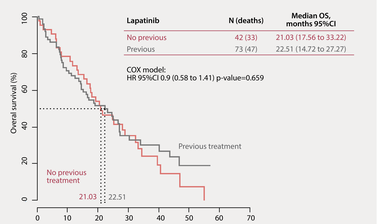


Figure 5. Time to progression according HR status

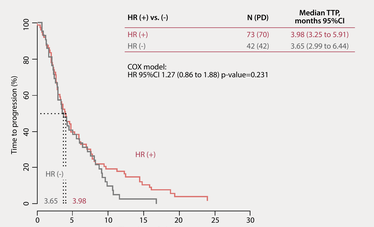


Figure 6. Overall survival according HR status

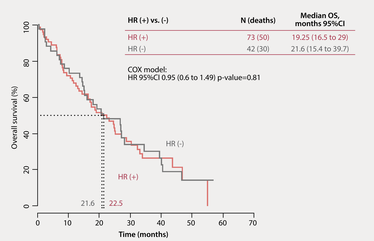


Figure 7. Time to progression according number of previous T lines (<3 vs. >= 3)

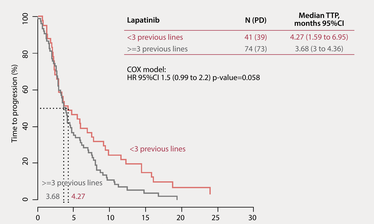


Figure 8. Time to progression according presence of central nervous system metastases

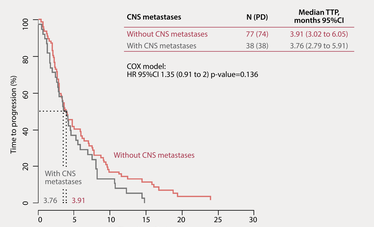
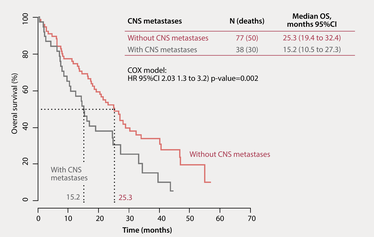


Figure 9. Overall survival according presence of central nervous system metastases



CONCLUSIONS

- Dual blockade seems safe and active in heavily pretreated patients. The combination remains active among patients progressing on prior L.
- Future research may focus on the ability of endocrine therapy to increase activity among HER2+/HR+ patients.

REFERENCES

1. Blackwell KL, Burstein HJ, Storniolo AM, et al: Randomized Study of Lapatinib Alone or in Combination With Trastuzumab in Women With ErbB2-Positive, Trastuzumab-Refractory Metastatic Breast Cancer. J Clin Oncol 2010;28(7):1124-1130.
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ACKNOWLEDGMENTS

* GlaxoSmithKline