

Efficacy and Safety of Pertuzumab in Metastatic Breast Cancer Patients in a Real-World Setting: Results from the SUPER-GONO (Gruppo Oncologico Del Nord Ovest) Study

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1. Abstract

1.1. Background: Real-world data have the potential to demonstrate the applicability of the results of randomized studies in the general population. SUPER trial was conducted in order to assess the activity, the efficacy and the safety of the combination of pertuzumab, trastuzumab and chemotherapy in clinical practice.

1.2. Material and Methods: Patients diagnosed with HER2 positive metastatic breast cancer (mBC) and treated with pertuzumab, trastuzumab and chemotherapy were accrued at 18 Italian hospitals. Data were retrospectively collected in the time frame between 2016, and prospectively collected thereafter.

1.3. Results: 342 HER2 positive mBC were accrued. 172 patients had relapsed disease and 56.4% of them received neo/adjuvant trastuzumab and chemotherapy.

tuzumab. 205 patients received docetaxel. Objective response rate was 76.3% (95%CI:71.4–80.7). Median progression free survival (PFS) and overall survival (OS) were 24.3 (95%CI:20.0–28.9) and 70.2 months (95%CI:61.4–79.0) respectively. Triple positive patients treated with endocrine therapy in addition to pertuzumab and trastuzumab maintenance had a significant longer PFS and OS than patients who did not. mPFS was 31.2 and 13 months respectively (95%CI:0.33–0.66; $p<0.001$) and mOS was 72.3 and 56.8 months respectively (95%CI:0.36–0.92; $p=0.02$). Pretreatment with trastuzumab did not hamper the outcome. In addition, maintaining the dual blockade inhibition at disease progression with the same chemotherapy partner or alternative endocrine agent leading to further benefit.

1.4. Conclusions: SUPER suggests that results of first-line treatment with pertuzumab, trastuzumab and chemotherapy in unselected patients are consistent with findings from CLEOPATRA trial.

Moreover, as expected from real-world evidence, new insights have emerged.

2. Introduction

HER2 positive tumors represent about 15% of all breast cancer diagnoses and are characterized by higher aggressiveness and worse prognosis compared to other subtypes [1, 2]. The introduction of trastuzumab has significantly improved the outcome of HER2 positive breast cancer patients both in the adjuvant and advanced setting [3-8]. Pertuzumab, a humanized monoclonal antibody that binds to the extracellular domain II of HER2, further improved the outcome of metastatic Breast Cancer patients (mBC). In the CLEOPATRA randomized phase III study trial patients previously untreated for advanced disease were randomly assigned to receive the combination of docetaxel, trastuzumab and pertuzumab or docetaxel trastuzumab and placebo. The dual HER2 blockade plus CT significantly increased both Progression Free Survival (PFS) and Overall Survival (OS) [9-11]. Pertuzumab and trastuzumab combination was also evaluated in a small phase II trial in which docetaxel was substituted with paclitaxel and in the larger PERUSE trial, in which anti HER2 therapy was associated with paclitaxel, docetaxel or nab-paclitaxel [12-14]. The addition of pertuzumab to trastuzumab and paclitaxel showed remarkable outcome results with reduced toxicity in comparison to docetaxel. However, in the CLEOPATRA trial, a minority of patients had received adjuvant trastuzumab, which is now the standard treatment for the vast majority of HER2 + early breast cancer.

SUPER is a retrospective and prospective observational study collecting data of HER2 positive metastatic breast cancer patients treated with chemotherapy, trastuzumab and pertuzumab in a real-world setting, aimed at evaluating whether the CLEOPATRA results are reproducible outside the context of a clinical trial.

3. Methods

The SUPER trial is an observational, retrospective and prospective

multicenter study aimed at evaluating the efficacy and safety of the association of CT plus trastuzumab and pertuzumab in a real-world setting, carried out at 18 Italian hospitals.

4. Study Design

4.1. Aims

The primary aim was the evaluation of the efficacy of pertuzumab based treatment, Progression Free Survival (PFS) was the primary study endpoint. Secondary aims included: 1) the activity— namely the Objective Response Rate (ORR), the Disease Control Rate (DCR), and the Clinical Benefit Rate (CBR); 2) the outcome in pre-defined subsets of patients according to prior adjuvant trastuzumab and endocrine therapy maintenance during dual blockade maintenance; 3) the safety of the combination; and 4) the Overall Survival (OS).

4.2. Patients

All patients treated with a combination of CT, trastuzumab and pertuzumab since the availability of pertuzumab in Italy (2012) were enrolled. Data were retrospectively collected in the time frame between pertuzumab availability and study approval in 2016, and prospectively collected thereafter. Docetaxel and paclitaxel were administered at 75 or 100 mg/m² intravenously every 3 weeks, and 80 mg/m² intravenously weekly, respectively. Notably, 3 administration of weekly paclitaxel were considered as 1 cycle of chemotherapy. Pertuzumab and trastuzumab were administered intravenously every 3 weeks at their approved doses (pertuzumab 840 mg loading dose at the first cycle, 420 mg at following cycles, trastuzumab 8 mg/kg loading dose at the first cycle and 6 mg/kg at subsequent cycles). Treatment was continued until disease progression, unacceptable toxicity or patient refusal. Chemotherapy dose reductions or cycles delays were reported. Tumor response was assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) criteria version 1.1. [15]. every 12 weeks according to rules of the Agenzia Italiana del Farmaco (AIFA) registry. Toxicity was evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, version 4). All patients underwent echocardiogram for Left Ventricular Ejection Fraction (LVEF) evaluation at baseline and every 3 months as per indication. The study was approved by local Ethical Committee of participating Institutions. All patients signed an informed consent.

4.3. Statistical Analyses

The primary endpoint was the evaluation of the PFS defined as the time elapsed between the first cycle of therapy and disease progression or death from any cause, whichever occurred first, or at the date of the last follow-up for censored patients. Secondary endpoints included OS, defined as the time elapsed between the first cycle of therapy and death from any cause, or the date of the last follow-up for censored patients. ORR was defined as the amount of Complete Response (CR) and Partial Response (PR). DCR was defined as the sum of CR, PR and disease stabilization

(SD). CBR was defined as the occurrence of CR, PR or long-lasting (≥ 24 weeks) disease stabilization. The PFS and OS were estimated based on the Kaplan-Meier method [16]. The Log-rank test [17] was used to compare PFS differences in prespecified subsets of patients. A p value lower or equal than 0.05 was considered as significant in all statistical analyses.

5. Results

From March 2016 to February 2019, 347 HER2 positive metastatic breast cancer patients treated with the combination of CT, pertuzumab and trastuzumab were accrued. Five patients were excluded from the evaluation due to incomplete data. Therefore, the final analyses were conducted on 342 patients, 236 patients (69%) in the retrospective cohort and 106 patients (31%) in the prospective cohort. The main patients' characteristics are summarized in Table 1.

Briefly, the median age was 55 years (range 19-80), the majority of patients had good performance status and about two third of them had hormone receptor positive disease. Visceral disease was present in 219 patients (64%) and the median number of metastatic sites was 3 (range: 1–8). Fourteen patients (4.1%) presented Central Nervous System (CNS) involvement. 170 patients (49.7%) had de novo metastatic disease and 97 of 172 patients (56.4%) with relapsed disease had received prior neo/adjuvant trastuzumab. 58 patients (17%) were 70 years or older: among them, visceral disease was present in 32 patients (55.2%), while 20 patients (34.5%) had both visceral and non-visceral disease and 25 (43.1%) had non visceral involvement only.

The median Disease-Free Interval (DFI) was 56.9 months (range, 3.6-286.8 months). Regarding the type of CT, 205 patients (59.9%) were treated with docetaxel, 136 (39.8%) received weekly paclitaxel and 1 patient received vinorelbine. In particular, weekly paclitaxel was the chemotherapy backbone in the majority (72.4%) of patients aged >70 years.

Overall, 2,360 cycles of chemotherapy were administered, and the patients were exposed to a median of 6 cycles (range: 1–24). The CT dose was reduced in 177 cycles (7.5%) and 48 patients (14%) needed a dose reduction mainly due to toxicity. The treatment was delayed in 49 cycles (2.1%) and in 34 patients (9.9%) mainly due to: (1) toxicity (24 patients, 7%, including 3 pts with asymptomatic decline of left ventricular ejection fraction); (2) patient request (6 patients, 1.7%); (3) bone radiotherapy (2 patients, 0.6%); (4) flu-like syndrome (2 patients, 0.6%). At the end of the planned CT, 320 patients (93.5%) underwent maintenance with pertuzumab and trastuzumab. The median duration of the maintenance therapy was 24 months (range: 1.4–78.1). Overall, 235 patients (68.7%) had triple positive disease, 177 (75.3%) received maintenance hormonal therapy along with pertuzumab and trastuzumab at the time of chemotherapy discontinuation.

Table 1: Patients' characteristics

	Patients N. 342 (%)
Age- yr	
Median (range)	55 (19-80)
Disease status at study entry	
Relapsed disease	172 (50.3)
De novo disease	170 (49.7)
ECOG performance status	
0	269 (78.7)
1	54 (15.8)
2	19 (5.5)
Median (range)	0 (0-2)
HER2 status assessed by IHC or FISH	342 (100)
Hormone Receptor status at study entry	
Positive	235 (68.7)
Negative	107 (31.3)
Hormone receptor status at diagnosis*	
Positive	130 (75.6)
Negative	40 (23.2)
Unknown	2 (1.2)
Neo/Adjuvant therapy*	
CT alone	50 (29.1)
CT+ trastuzumab	97 (56.4)
No	25 (14.5)
Adjuvant endocrine therapy **	
Yes	120 (93.0)
No	9 (7.0)
Metastatic disease	
Visceral	219 (64.0)
Non visceral	97 (28.4)
Both	150 (43.9)
Metastatic sites	
1	85 (24.8)
2	83 (24.3)
3	81 (23.7)
≥ 4	93 (27.2)
Median (range)	3 (1-8)
Most common metastatic sites	
Bone	180 (52.6)
Liver	140 (41.0)
Lung	108 (31.6)
Soft Tissue	247 (72.2)
Pleura	27 (7.9)
CNS	14 (4.1)

*Data on 172 patients; ** On 129 HR+ patients at diagnosis

CNS: Central Nervous System

5.1. Activity

Overall, the ORR and CBR in the whole population were 76.3% (95%CI: 71.4–80.7) and 90.9% (95%CI: 87.4–93.8), respectively (Table 2). The ORR related to the different companion drug was 78.5% (95%CI 72.3–84.0) and 72.8% (95%CI: 64.5–80.1) with docetaxel and weekly paclitaxel, respectively (p=0.22). However, in the 172 relapsed patients the ORR was 69.8% (95%CI: 63.3–76.5), and was 82.9% (95%CI: 76.4–88.3) in patients with de novo metastatic disease (p=0.006). In the elderly cohort, the ORR was 67.2% (95%CI: 53.7–79.0).

Table 2: Activity

Response	Patients N. 342 (%)
Objective response	261 (76.3)
Complete response	79 (23.1)
Partial response	182 (76.3)
Stable disease	52 (15.2)
Progressive disease	24 (7.0)
Not evaluable	5 (1.5)
Clinical benefit rate	309 (90.3)
Disease control rate	313 (91.5)

5.2. Efficacy

At a median follow-up of 40.8 months (1.1–94.7+ months), 234 PFS events and 124 deaths have been recorded. The median PFS in the whole population was 24.3 months (95% CI: 20.0–28.9). The median OS in the entire cohort was 70.2 months (95% CI: 61.4–79.0) (Figure1). In patients who received prior neo/adjuvant trastuzumab, the median PFS and OS were 19.0 months (95% CI: 13.7–24.3) and 59.7 months (95% CI: 39.8–79.6), respectively, demonstrating the efficacy of the treatment also in this pretreated

population. However, a significant difference in the median PFS and OS was observed among patients with prior exposure to trastuzumab compared to trastuzumab naïve patients, being 28.7 months (95% CI: 21.7–38.7; HR=0.64; 95% CI: 0.49–0.85; p=0.002) and not reached, respectively, in the latter group (HR=0.69; 95% CI: 0.48–0.98; p=0.04) (Figure 2). Furthermore, we detected significantly longer PFS and OS in patients with triple positive disease exposed to the combination of endocrine therapy, pertuzumab and trastuzumab as maintenance therapy compared to patients who did not receive hormone therapy. The median PFS was 31.2 months (95% CI: 24.9–37.5) in the cohort of patients treated with endocrine therapy in addition to dual blockade maintenance compared to 13.0 months (95% CI: 10.1–15.9) in those patients who received only pertuzumab and trastuzumab (HR=0.47; 95% CI: 0.33–0.66; p<0.001). The Median OS was 72.3 months (95% CI not reached) and 56.8 months (95% CI not reached) in the two groups, respectively (HR=0.58; 95% CI: 0.36–0.92; p=0.02).

No significant difference was observed between paclitaxel and docetaxel in terms of PFS and OS.

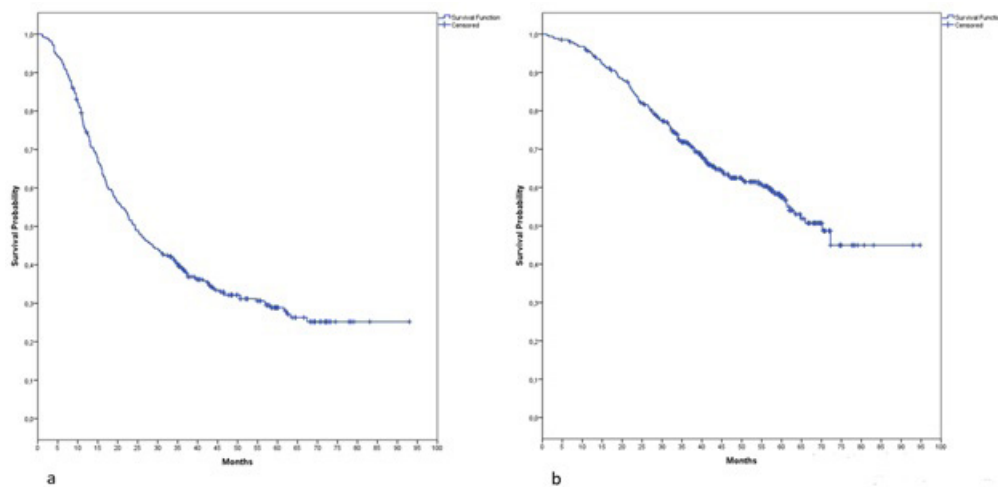


Figure 1: Progression-Free Survival (a) and Overall Survival (b) in the overall population.

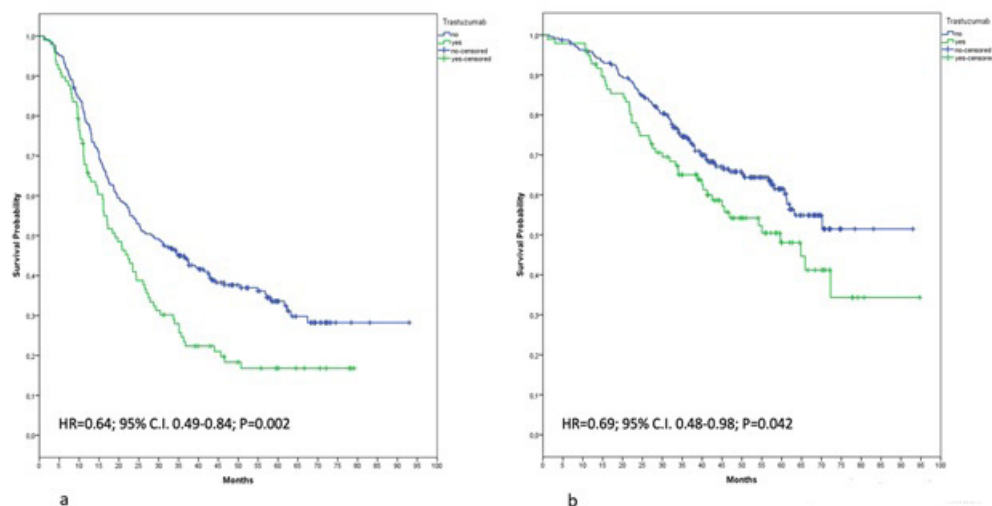


Figure 2: Progression-Free Survival (a) and Overall survival (b) according to exposure to adjuvant trastuzumab

5.3. Safety

Adverse events are reported in Table 3. No new safety concerns about the association of CT plus pertuzumab and trastuzumab emerged from our cohort of real-life patients. The most frequent adverse events were asthenia, diarrhea and mucositis, mostly grade

1 or 2. Thirty-two patients (9.3%) experienced cardiac toxicity, which led to discontinuation of anti HER2 therapy in 17 of them (4.9%). Twenty-three patients (6.7%) had LVEF decline and 14 of them (4.1%) were symptomatic.

Table 3: Adverse Events

Advers Events	All grades No. (%)	Grade 3 No. (%)	Grade 4 No. (%)
Leucopenia	84 (24.6)	15 (4.4)	3 (0.9)
Neutropenia	90 (26.6)	8 (2.3)	18 (5.3)
Febrile Neutropenia	11 (3.2)	11 (3.2)	-
Anemia	106 (31)	3 (0.9)	-
Diarrhea	162 (47.4)	11 (3.2)	1 (0.3)
Asthenia	212 (62)	6 (1.7)	-
Mucosal inflammation	110 (32.2)	2 (0.6)	-
Nausea	39 (11.4)	4 (1.2)	-
Peripheral neuropathy	135 (39.5)	5 (1.5)	-
Arthro-myalgia	26 (7.6)	-	-
Rash	21 (6.1)	-	-
H-F Syndrome	50 (14.6)	4 (1.2)	-
Alopecia	172 (50.3)	-	-
Dyspnea	20 (5.8)	5 (1.5)	-
ALT increase	43 (12.6)	-	1 (0.3)
AST increase	46 (13.5)	2 (0.6)	-
Nail disorders	33 (9.6)	2 (0.6)	-
Pruritus	13 (3.8)	-	-
Cardiac toxicity	31 (9.1)	16 (4.7)	-
Left ventricular ejection fraction drop	23 (6.7)	11 (3.2)	-

5.4. Long Term Outcomes

At the time of the present analysis (October 2020), 89 patients (26%) were still on pertuzumab and trastuzumab maintenance. Fifty-five of them (16%) were receiving endocrine therapy together with monoclonal antibodies, and 24 patients (7%) discontinued pertuzumab during maintenance due to toxicity. Overall, HER2 double blockade maintenance was discontinued in 253 patients (74%). 231 patients (67.5%) experienced disease progression, 21 (6.1%) discontinued dual blockade maintenance and 1 patient was receiving maintenance with trastuzumab alone. These patients were actually free from progression. Apart from progression, the reasons for discontinuation of the maintenance at any time included persistent and symptomatic drop of LVEF (12 patients, 3.5%), toxicity (13 patients, 3.8%), medical decision (9 patients, 2.6%), refusal or patient decision (7 patients, 2%), stroke (2 patients, 0.6%), deterioration of PS (2 patients, 0.6%), diagnosis of acute lymphatic leukemia (1 patient, 0.3%) and death (1 patient, 0.3%). Of these latter group of patients 25 patients went on disease progression. At disease progression all but 18 patients (7.8%) were given second line therapy. 145 patients (62.8%) received T-DM1, 22 (9.5%) the association of lapatinib and capecitabine, 16 (6.9%) trastuzumab plus chemotherapy or endocrine therapy, and 17 (7.3%) were treated with CT or were enrolled in clinical trials. 6 patients (2.6%) who experienced CNS progression as unique site of disease were treated with local therapy and went on maintenance with pertuzumab and trastuzumab. Interestingly, 7 patients (3%) who had developed metastases outside the CNS underwent rechallenge with docetaxel plus monoclonal antibodies or cross-clinicsofoncology.com

ing to another endocrine therapy plus HER2 dual blockade. All of them benefited again from the therapy.

6. Discussion

Our retrospective and prospective analysis performed on patients from a real-world setting confirms the findings of the CLEOPATRA trial in terms of ORR, PFS and OS, with no new safety concerns. Most importantly, additional information not clearly reported in the pivotal study emerges from our analysis. First, in our series, triple positive patients received endocrine therapy in association with pertuzumab and trastuzumab maintenance, which was not allowed in the CLEOPATRA trial. This combination led to better efficacy results in patients who underwent both endocrine and anti HER2 maintenance therapy in comparison to endocrine responsive patients treated with anti HER 2 therapy alone, as demonstrated by a significantly longer median PFS in the former group (31.2 vs. 13.0 months, respectively, $p < 0.001$). This advantage resulted in longer OS (72.4 months vs. 65.8 months, respectively, $p = 0.01$). Given the cross-talk between HER2 and ER, HER2 suppression might strengthen and restore the ER pathway [18]. Therefore, the co-administration of endocrine therapy with HER2 blockade contributes to a more profound inhibition leading to better outcome [18-20]. Other authors have reported similar findings in clinical practice [21, 22], underlining the importance of the inhibition of the ER pathway in HR-positive HER2 positive mBC. This issue is also supported by the 5th ESO-ESMO international consensus guideline for advanced breast cancer ABC-5 [23].

Second, in our cohort, 172 patients had relapsed disease and 97 of

them (56.4% of the relapsed population and 28.4% of the entire group) received trastuzumab as part of their adjuvant treatment. Despite prior exposure to trastuzumab seemed not to affect subsequent therapy with pertuzumab and trastuzumab, the median PFS and OS in trastuzumab naïve patients were significantly longer than in patients exposed to adjuvant trastuzumab. In CLEOPATRA, only 47 patients (11.7%) treated with dual blockade received trastuzumab as neo/adjuvant treatment [9]. No negative findings were described in the trial, however, the small number of patients exposed to adjuvant trastuzumab limited the applicability of the results to the general patient population that is usually exposed to therapy with trastuzumab in the early setting. Gamucci et al. [22] reported a non-significant difference in the median PFS between patients naïve and exposed to prior trastuzumab (23 and 17 months, respectively, $p=0.10$), however a significant longer OS was observed in the trastuzumab naïve group ($p=0.02$). Another report did not describe a negative impact of neo/adjuvant trastuzumab on the efficacy of pertuzumab. However, no difference in the outcome between the two groups was observed [21].

Third, as reported by others [12, 14, 21, 22, 24, 25], the CT backbone has not a significant influence on the outcome. In the advanced setting, clinicians should choose the less toxic agent in order to preserve patients' quality of life. To this aim, paclitaxel may be preferable, as demonstrated by the PERUSE trial [14]. Moreover, the duration of CT does not hamper the outcome [26].

An intriguing issue coming out from our analysis is the challenge with the same CT partner or with alternative endocrine agent at disease progression. This strategy allows to prolong the inhibition with dual blockade while maintaining activity, leading to a delay in the use of subsequent therapy exploiting completely the performance of the drug. This aspect deserves further research.

Finally, there is uncertainty about the direct transferability of clinical trial results in a real-world setting, due to the strict patient selection criteria and the difficulty to apply them to the general patient population. In contrast, real-world studies include a wide proportion of patients who are excluded from registration studies, such as patients with brain metastases. Therefore, real-world studies might mimic phase IV trials. In the past, many real-world studies have been conducted to confirm data of pivotal phase III studies [27-29].

One important limitation of our study is its observational nature, albeit one third of our population was treated prospectively. Response evaluation, in clinical practice, could not be properly evaluated. Tumor assessment was evaluated every 3 months according to AIFA (Agenzia Italiana Farmaco) registry rules. On the other hand, our study also has some clear strengths, as it supports the use of endocrine therapy in addition to anti HER2 maintenance in hormone receptor positive patients and reinforces the available data regarding activity and efficacy in patients previously exposed

to adjuvant trastuzumab. Moreover, it suggests the possibility to maintain dual blockade inhibition at disease progression with the same CT partner or changing endocrine agent.

7. Conclusions

In conclusion, the SUPER study exemplifies the utility of real-life studies and, to the best of our knowledge, it is the largest real-life study in HER2 positive metastatic breast cancer to provide evidence that the treatment with taxane plus pertuzumab and trastuzumab is feasible, active and effective, without any additional toxicity in unselected patients.

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