 doi:10.20944/preprints202207.0371.v1

Article

Trastuzumab Biosimilar ABP 980 Plus Pertuzumab and Docetaxel in the Therapy of Metastatic Breast Cancer: Real World Experiences from the National Research Institute of Oncology in Warsaw

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Abstract

Background: Human epidermal growth factor receptor 2 (HER-2) overexpression can be found in 15-20% of breast cancers, and it strongly correlates with aggressive clinical behavior and adverse prognosis. The first-line treatment for HER-2 positive metastatic breast cancers is the combination of trastuzumab, pertuzumab, and taxane (PTH). ABP 980 is a biosimilar of the innovator trastuzumab and is characterized by highly comparable effectiveness.

Methods: The group of 61 patients with HER-2 positive MBC received biosimilar ABP 980 plus pertuzumab and docetaxel from November, 18, 2018 to December, 24, 2019. The response to therapy, overall survival (OS), progression-free survival (PFS), metastases, and adverse effects among patients were determined and analyzed.

Results: Initially, 42 women responded partially to the treatment and their median PFS was 27 months. Median PFS for the whole group was 18 months. Cardiotoxicity of treatment was noticed in all patients in the form of the reduction in left ventricular ejection fraction but only in 2 cases, it was the reason for withdrawing from therapy.

Conclusion: Biosimilar ABP 980 is registered in the same indications as the innovator trastuzumab and their effectiveness, as well as side effects, are comparable. The costs of biosimilar make the therapy more accessible and thus more patients with MBC around the world can receive relevant treatment.

Keywords: biosimilar; trastuzumab; metastatic breast cancer; HER-2 positive; PTH therapy

Introduction

Breast cancer (BC) is the most common type of cancer in the world, and despite the undoubted advances in methods used for cancer diagnoses and treatment, it has a high mortality rate [1, 2]. The human epidermal growth factor receptor 2 (HER-2) is overexpressed in 15-20% of breast cancers [2-5], which defines BC as strongly associated with aggressive clinical behavior, high recurrence rates or metastases and worse prognosis [2-4]. HER-2 levels correlate strongly with carcinogenesis and are associated with increased resistance to some chemotherapeutic drugs [5,6]. A huge breakthrough in the treatment of this biological subtype of BC has been the development of anti-HER2 targeted therapies. The first drug of this type is the humanized monoclonal antibody Trastuzumab [7]. It was approved for use in patients with HER2-positive metastatic breast cancer (MBC) by the U.S. Food and Drug Administration (FDA) in 1998 and by the European Medicines Agency (EMA) in 2000 [8,9]. In 2006, it was approved by the EMA and FDA for adjuvant therapy, and in 2011 for neoadjuvant therapy [8,9]. The past two decades have seen rapid development of anti-HER2 therapies, which has significantly improved the prognosis in this group of patients [10,11]. Still, trastuzumab and pertuzumab in combination with taxane (PTH) remain the standard first-line therapy for most MBC patients [4, 12]. The current guidelines are based on the results of the randomized phase 3 CLEOPATRA study, in which the use of two anti-HER2

 doi:10.20944/preprints202207.0371.v1

drugs, pertuzumab, and trastuzumab in combination with chemotherapy, was proven to be more effective than the use of trastuzumab plus the chemotherapy, both in terms of response rates, increasing the median PFS and median OS [13,14].

For more than 5 years now, biosimilars have been on the market in addition to the original Herceptin®. Biosimilars are biological products that are highly like a referenced anti-HER2 antibody in terms of their structure and functionality and have demonstrated similarity to trastuzumab in terms of safety, clinical efficacy, and tolerability [15, 16]. While the cost of therapy with the original product can be a problem in some low-income countries, the use of biosimilars involves lower financial expenses, providing easier access to BC therapies worldwide [16-18]. The guidelines for registration of biosimilars assume their registration in all indications that the original product has, provided the biosimilar product is like a registered originator product (i.e., reference product) in terms of safety, efficacy, and immunogenicity in at least one indication [19,20]. One of the biosimilars is the monoclonal antibody ABP 980 (Kanjinti), which is approved for the treatment of HER2-positive early and metastatic breast cancer and metastatic gastric cancer [21,22]. APB 980 has been compared with Herceptin® for the neoadjuvant therapy of early breast cancer (EBC). However, the efficacy and safety of this drug in combination with pertuzumab in MBC have not been assessed.

Aim

The present study was conducted to evaluate the toxicity and efficacy of ABP 980 in combination with pertuzumab and docetaxel for first-line therapy of HER2-positive MBC at the National Research Institute of Oncology in Warsaw, the Breast Cancer, and Reconstructive Surgery Department.

Ethics statement

The study protocol was approved by the Ethics Committee of Maria Sklodowska-Curie National Research Institute of Oncology (No 22/13/2021). The study was performed per Good Clinical Practice standards and the ethical principles that have their origin in the Declaration of Helsinki. All patients provided informed consent for use of their data for research purposes.

Materials and methods

We analyzed medical records of breast cancer patients who were treated with a PTH regimen with APB 980 (Kanjinti®) as first-line therapy of MBC from Nov/28/2018 to Dec/24/2019.

All patients met the following criteria: ECOG 0-1 performance status, histopathological diagnosis of HER2-positive MBC, and baseline left ventricular ejection fraction (LVEF) of ≥50%. The key exclusion criteria included relapse within 1 year of the last dose of previous adjuvant (including neoadjuvant) any-HER2 treatment.

All patients received the PTH regimen (docetaxel, trastuzumab, and pertuzumab) at the following doses: docetaxel 75 mg/m2, once every 3 weeks (6- 8 cycles), biosimilars trastuzumab: loading dose 8 mg/kg followed by 6 mg/kg intravenously, pertuzumab: loading dose 840 mg followed by 420 mg intravenously, once every 3 weeks to disease progression or unacceptable toxicity. All patients with positive hormone receptors also received hormone therapy after the end of docetaxel.

All patients were evaluated for response every 12 weeks using a CT scan according to RECIST 1.1 criteria.

Adverse events were assessed according to the Common Terminology Criteria for Adverse Events, version 4.0 [23]. Echocardiography was used to monitor LVEF; it was performed before the start of treatment and then every 12 weeks during the therapy.

Statistical analysis

The normality of the distribution of the individual parameters evaluated in the study was verified using the Shapiro-Wilk test. In the case of normal distribution, Student's t-distribution test was used to compare the mean values of independent variables. For the other parameters without normal distributions, appropriate methods of statistical analysis were selected based on non-parametric tests. The Mann-Whitney U test was used to compare numerical variables between the two groups observed. A Kruskal-Wallis test was used for the three groups. A non-parametric Wilcoxon signed-rank test was used to check for the differences between the results of the various parameters analyzed in the study group at different periods (dependent variables). A paired t-test was used to analyze two dependent variables with normal distributions. A linear mixed-effects model was used to examine the relationship between the variables. All calculations and graphs were performed using the R statistical package version 4.0.2.

Results

The inclusion criteria for the study were met by 61 patients. The median age of the entire group was 57 years. Most patients (75.4%) were below the age of 65. Most patients (78.3%) were diagnosed with luminal B HER 2 - positive cancer.

 doi:10.20944/preprints202207.0371.v1

More than half of the patients (55.7%) had previously received systemic therapy for EBC, of which 40% were treated with trastuzumab. Most cases (65.6%) were diagnosed with multiple metastases. Only four patients (6.6%) had CNS metastases. The characteristics of the patients are shown in Table 1.

Treatment toxicity

No grade 4 toxicity was found. No deaths due to toxicity were observed. There were also no unexpected toxicities that had not been described concerning treatment with the PTH regimen in the CLEOPATRA study. The most common side effects were weakness (52.4%), diarrhea (39%), neutropenia (36%), and anemia (32.8%). It should be noted that diarrhea was more frequently observed in patients aged 65 and older (53.3% vs 34.7%), of which 2 patients (13.3%) had grade 3 diarrhea. The toxicity data are shown in Table 2.

LVEF analysis at selected time points

LVEF values were monitored in the study. There were no significant differences in baseline LVEF values which would depend on the age of the patients (Figure 1.). LVEF before the therapy averaged 63.67% whereas the value of the last LVEF measure was 60.77%. The LVEF results are shown in Table 3. and Figure 2. No correlations between patients' LVEFs and BMIs were observed. Also, type II diabetes had no effect on LVEF values during the therapy.

An LVEF reduction of 10-15% was observed in 7 patients (11.5%), and a <50% reduction affected only 2 patients (3.3%). Other cardiac problems, supraventricular arrhythmias, were observed in 4 patients (6.5%).

CNS metastases

A statistical analysis of risk factors for the development of central nervous system (CNS) metastases was performed. The only correlation observed was the one with the absence of estrogen receptor (ER) expression. The CNS metastases patients had a median PFS of 7 months, while the rest of the group had a median PFS of 12 months (Table 4).

Response to treatment

68.9% (N=42) of patients had a partial response (PR), 23% (N=14) achieved stabilization of the disease (SD), and there were no cases with complete regression (CR). 8.2% (N=5) of patients had no response whatsoever (PD in the first response assessment). The most common reason for therapy discontinuation was disease progression - 39 patients (63.9%), two patients discontinued therapy due to cardiotoxicity (3.3%), and one patient discontinued therapy for other reasons (1.7%). At the time when the data were summarized (April /21/2022), 19 patients (31.1%) were continuing the therapy with trastuzumab plus pertuzumab.

Survival analysis

The median PFS in the study group was 18 months (Figure 3), and the median OS was not reached (Figure 4).

The median OS was analyzed depending on the response achieved; the median OS for the subgroup of patients who did not respond to first-line therapy was achieved and totaled only 19 months, despite using subsequent lines of anti-HER2 therapy (trastuzumab-emtansine, lapatinib plus capecitabine, trastuzumab deruxtecan), while the median OS was not achieved in the subgroups with PR or SD. (Figure 5).

Discussion

Breast cancer with high HER2 expression levels is associated with worse prognosis and the disease progressing more dynamically. Significant improvements in therapy outcomes for this biologic subtype were achieved when HER2 blockers were introduced into routine management. The dual antibody blockade of HER2 with pertuzumab, trastuzumab plus taxanes has been shown to significantly increase the median OS in first-line therapy of MBC patients [13,14]. In the CLEOPATRA study, the median OS was 57.1 months and the median PFS was 18.7 months [14]. In our study, the mOS had not been reached yet, while the mPFS was 18 months.

The therapy described in the CLEOPATRA study has been duplicated in several other studies, including those involving Asian populations (the Japanese COMACHI study and the Chinese PUFFIN study); the results thereof were consistent with the CLEOPATRA study results. The median PFS achieved in these studies ranged between 14.5 and 27.8 months [24-28]. Equivalent results were also presented in a study evaluating a trastuzumab biosimilar (SB3); the mPFS obtained in this study was 12.7 months [29]. Table 5 shows a comparison of the results of the most frequently quoted studies evaluating the efficacy and safety of PTH therapy.

In our study, a significant percentage of patients (78.3%) were found to have the ER receptor in cancer cells. Patients with HER2-positive, HR-positive breast cancer also prevailed in other studies, but the percentage of those patients was lower (47-70%), which could translate into a higher ORR. A significant percentage of patients in our study had previously received systemic therapy for early breast cancer (55.7%), while in other studies, except for the Chinese study [28] and the SB3 evaluation study [29], this group of patients usually did not exceed 50% (27.8%- 48%). These differences

in the structure of the patient group also could potentially translate into slightly poorer therapy outcomes, as well as potentially higher rates of cardiotoxic complications.

Our follow-ups included only four patients with CNS metastases. These patients had significantly shorter mPFS compared to the rest of the population.

The median age of the patients evaluated in our study was 54 years. It is close to the median age of most similar studies (45-60, CLEOPATRA study - 54). Only 24.6% of the patients in our study were 65 or older. Their response to the therapy they received was like that of younger patients, but older patients were more likely to experience more intensive diarrhea and weakness, which is like the observations of other authors [36,37].

Undoubtedly, there were no significant cardiotoxic complications in the group we evaluated. The LVEF reduction below 50% was observed during the therapy in only 2 patients. This occurred in patients below the age of 65 who had previously received anthracyclines as part of their perioperative treatment. Similar cardiotoxicity results have also been reported by other authors [24,26,30]. When it comes to cardiotoxicity, it should be noted that no differences were found between patients' age groups. Other authors have also observed this [38].

Based on our observations, it can be concluded that the use of ABP 980 biosimilar in combination with pertuzumab and docetaxel is an effective and safe therapy for patients with generalized HER2 -positive breast cancer. Responses to therapy are like the results of therapy with the original trastuzumab in this indication. The safety of the therapy is also extremely high, with toxicities identical to the original regimen. This is a particularly important observation, given the pharmacoeconomic evaluations being conducted around the world and the search for opportunities to reduce the already exceedingly inflated cost of oncology treatment [39,40,41]. Our study results confirm that biosimilars used in oncology are not only safe and effective but also a less costly option of therapy [39,42].

This study has clearly had several restrictions, namely the group size was small, there was no control arm of the study, and the follow-up time was short. Nevertheless, it reflects the therapy conditions in daily clinical practice.

Conclusion

Our study is another report confirming the safety and efficacy of ABP 980 biosimilar in combination with pertuzumab and docetaxel in the first-line therapy of HER2-positive MBC patients. What should be emphasized is a low rate of serious complications observed among patients, especially a low rate of cardiotoxicity. The good tolerability of biosimilar therapy in the population of patients over the age of 65 has also been confirmed, which is important given the increasing incidence of breast cancer among this age group and the rising cost of oncological therapies.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest

The authors have declared no conflict of interest.

Fundings

None declared.

Acknowledgments

We thank BIOSTAT® (especially Magdalena Mrozinska) for any help with the statistical calculations.

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Table.1. Patient characteristics.

Variable	Parameter	Total	< 65 years old	≥ 65 years old
	N	61	46 (75.4%)	15 (24.6%)
Age [years]	Mean (SD)	56.39 (10.76)	48.2 (8.2)	68 (6)
	Median	57	49	68
	Range	28 - 76	28-64	65-76
ER	Positive	78.3% (N=47)	75.6%	86.7%
	Negative	21.7% (N=13)	24.4%	13.3%
PGR	Positive	60% (N=36)	53.3%	80%
	Negative	40% (N=24)	46.7%	20%
Single metastasis	Yes	34.4% (N=21)	37%	26.7%
	No	65.6% (N=40)	63%	73.3%

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Bone metastases	Yes	49.2% (N=30)	47.8%	53.3%
	No	50.8% (N=31)	52.2%	46.7%
Liver metastases	Yes	42.6% (N=26)	39.1%	53.3%
	No	57.4% (N=35)	60.9%	46.7%
Lung metastases	Yes	52.5% (N=32)	45.7%	73.3%
	No	47.5% (N=29)	54.3%	26.7%
CNS metastases	Yes	6.6% (N=4)	8.7%	0%
	No	93.4% (N=57)	91.3%	100%
Metastasis to soft tissues/lymph nodes	Yes	60.7% (N=37)	63%	53.3%
	No	39.3% (N=24)	37%	46.7%
Prior treatment due to EBC	Yes	55.7% (N=34)	39.1%	40%
	No	44.3% (N=27)	60.9%	60%
Prior treatment with trastuzumab	Yes	39.3% (N=24)	47.8%	40%
	No	60.7% (N=37)	52.2%	60%
Prior treatment with anthracyclines	Yes	41.0% (N=25)	53.5%	13.3%
	No	59.0% (N=36)	46.5%	86.7%
Adjuvant radiotherapy	Yes	32.7% (N=20)	36.4%	26.7%
	No	67.3% (N=41)	63.6%	73.3%
Diabetes	Yes	14.8% (N=9)	15.2%	13.3%
	No	85.2% (N=52)	84.8%	86.7%
BMI - breakdown	Normal value	34.4% (N=21)	34.8%	33.3%
	Overweight	29.5% (N=18)	30.4%	26.7%
	Obesity	36.1% (N=22)	34.8%	40%

Table 2. Treatment toxicity.

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Toxicity	Incidence (any grade)			Grade 3 or 4		
	Any	Patients <65	Patients ≥65	Any	Patients <65	Patients ≥65
Diarrhea	24 (39%)	16 (34.7%)	8 (53.3%)	2 (3.3%)	0	2 (13.3%)
Thrombocytopenia	13 (21.3%)	10 (21.7%)	3 (20%)	0	0	0
Neutropenia	22 (36%)	17 (37%)	5 (33.3%)	4 (6.5%)	2 (4.3%)	2 (13.3%)
Anemia	20 (32.8%)	16 (34.7%)	4 (26.7%)	2 (3.3%)	1 (2.2%)	1 (6.7%)
Fatigue	32 (52.4%)	19 (41.3%)	13 (86.7%)	2 (3.3%)	1 (2.2%)	1 (6.7%)
Neuropathy	12 (19.7%)	7 (15.2%)	5 (33.3%)	0	0	0
Mucositis	3 (4.9%)	2 (4.3%)	1 (6.7%)	0	0	0
Cardiac dysfunction	0	0	0	0	0	0

Figure 1. Comparison of LVEF distributions [%] - before therapy by age groups.

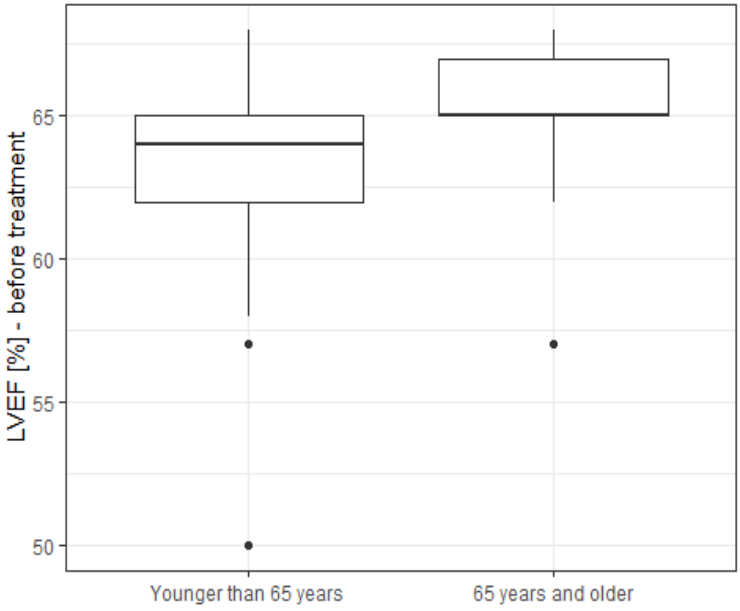

Table 3. Comparison of LVEF results [%]

Variable	Parameter	Before treatment			Last measurement during therapy		
		Total	< 65 years old	≥ 65 years old	Total	< 65 years old	≥ 65 years old
LVEF [%]	N	61	46	15	61	46	15

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	Mean (SD)	63.67 (3.43)	63.24 (4.08)	65 (2.67)	60.77 (4.1)	60.57 (4.42)	61.4 (2.97)
	Median (IQR)	65 (62 - 66)	64 (62-65)	65 (65-67)	61 (60 - 63)	61 (60-63)	62 (60-63)
	Range	50 - 68	50-68	57-68	46 - 67	46-67	55-65
10-15% LVEF decrease	Yes	-	-	-	11.5% (N=7)	6.5% (N=3)	26.7% (N=4)
	No	-	-	-	88.5% (N=54)	93.5% (N=43)	73.3% (N=11)
<50% LVEF decrease	Yes	-	-	-	3.3% (N=2)	4.3% (N=2)	0% (N=0)
	No	-	-	-	96.7% (N=59)	95.7% (N=44)	100% (N=15)
Other cardiac issues during treatment	Yes	-	-	-	6.5% (N=4)	6.5% (N=3)	6.7% (N=1)
	No	-	-	-	93.5% (N=57)	93.5% (N=43)	93.3% (N=14)
Other cardiac issues during the therapy	Yes	-	-	-	6.5% (N=4)	6.5% (N=3)	6.7% (N=1)
	No	-	-	-	93.5% (N=57)	93.5% (N=43)	93.3% (N=14)

Figure 2. Comparison of LVEF results [%] by the length of therapy.

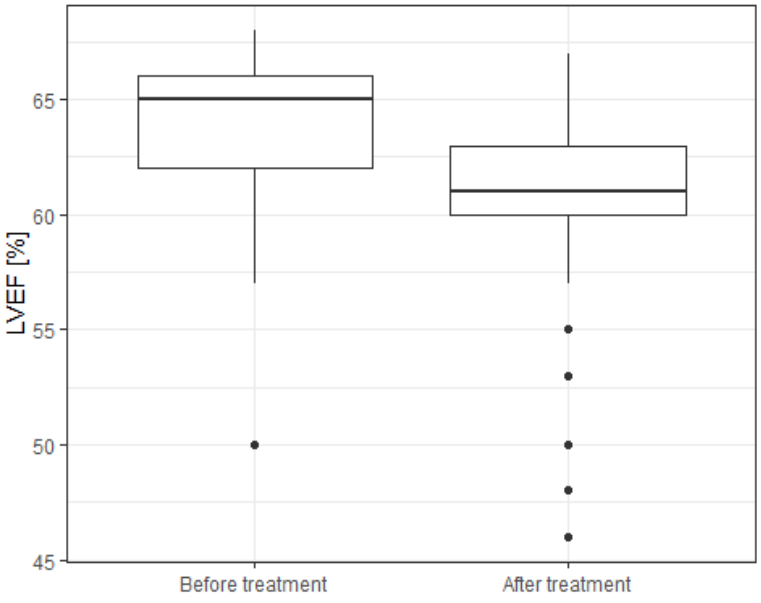

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Table 4. Comparison of CNS metastases variables

Variable	Parameter	CNS metastases (N=4)	No metastasis to the CNS (N=57)	test	p-value
ER	Positive	25% (N=1)	82.1% (N=46)	Fisher	0.029
	Negative	75% (N=3)	17.9% (N=10)		
Time to progression [months]	N	4	38	Student's t distribution	<0.001
	Mean (SD)	7 (0.82)	19.89 (9.19)		
	Median (IQR)	7 (6.75 - 7.25)	19 (7 - 20.75)		
	Range	6 - 8	1 - 28		

Figure 3. Kaplan-Meier curve for PFS.

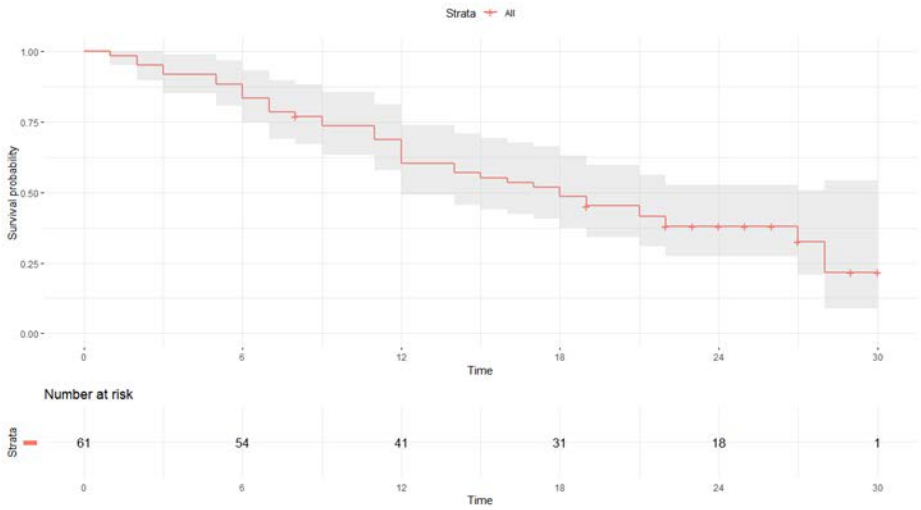

Figure 4. Kaplan-Meier curve for OS.

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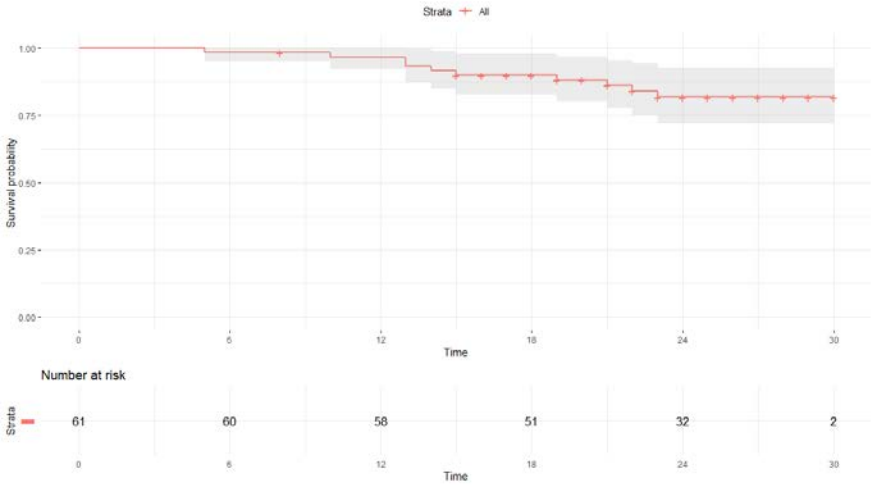

Figure 5. Kaplan-Meier curve for OS by the best response to treatment.

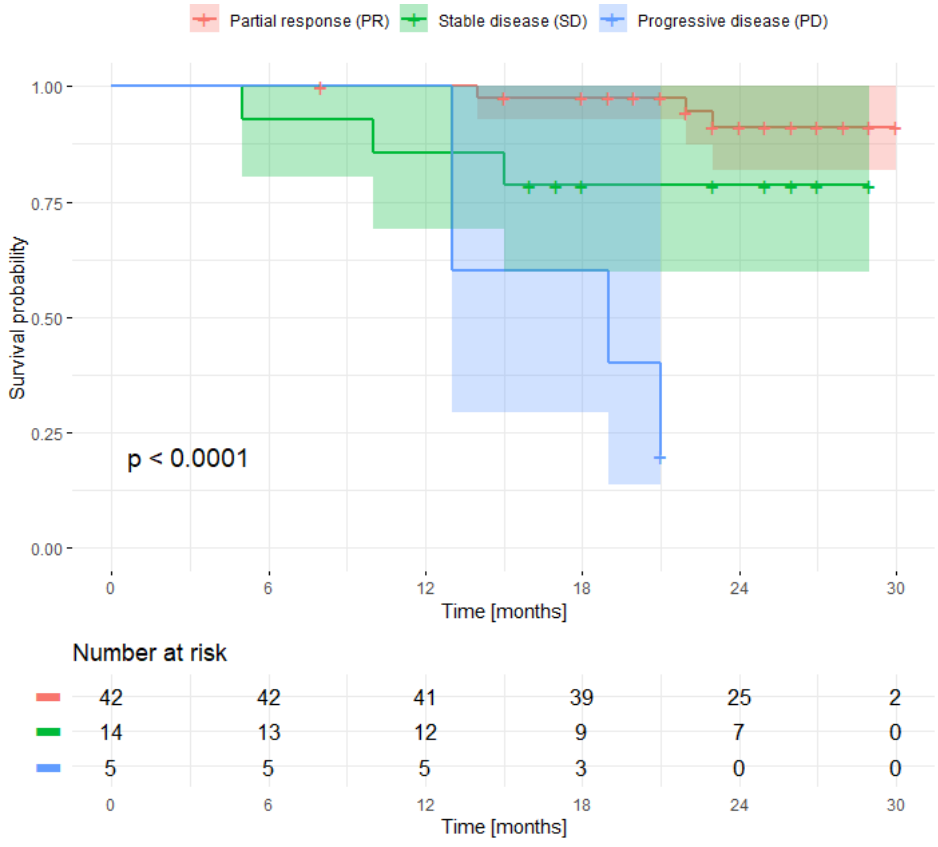

Table 5. Comparison of the results of studies evaluating PTH therapy.

Author, year of publication	Number of patients treated with pertuzumab + trastuzumab	Trastuzumab used	Age (Average)	Hormone receptor status, n (%)	Prior adjuvant or neoadjuvant therapy	Type of study	ORR	M follow-up	mPFS	mOS

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José Baselga et al. 2012 [35] Sandra M Swain et al. 2020 [14] CLEOPATRA	402	Herceptin	54	Positive – 47%, negative – 52.7% Unknown - 0.2%	Yes – 45.8% No -54.2%	randomized, double-blind, placebo-controlled, phase 3 trial,	80.2 %	99.9	18.7	57.1
Wei Fang Dai et al., 2022[30]	912	Herceptin (Roche)	58.2	Positive 51.1% Negative – 48.9%	Yes – 41% No – 59%	population-based retrospective comparative	N/A	N/A	N/A	40.2
Yong-Pyo Lee et al., 2022 [31]	228	N/A	60	Positive 54.3%, negative - 41.2% unknown - 4.3%	Yes - 29.3% No -70.6%	retrospective	86.8 %	28.7	19.1	58.3
Thomas Bechelot et al. 2019 [26]; David Miles et al. PERUSE, 2021 [32]	1436	Herceptin (Roche)	54	Positive - 64% Negative 35.6% unknown – 0.4%	Yes 27.8% No -72.2%	open-label, single-arm phase IIIb	79%	68.7	20.7	65.3
Kausar Suleman et al., 2021 [33]	75	Herceptin (Roche)	45	Positive 54.7% negative – 53%	Yes – 46% No – 54%	Retrospective, observational	74.7 %	36	36	N/A
Sreeram V. Ramagopalan et al., 2021 [34]	546	Herceptin (Roche)	59	Positive 61% Negative 31% unknown – 8.1	N/A	population-based retrospective	N/A	45.3	N/A	48.6
Masato Takahashi et al. COMACHI, 2021, [27]	132	Herceptin (Roche)	56.5	Positive - 54.5% Negative – 45.5%	Yes-28.8%, No- 71.2%	Prospective, phase IV	83.9 %	46.9	22.8	N/A
Binghe Xu et al. PUFFIN, 2020, [28]	122	Herceptin (Roche)	51	Positive - 56.6 Negative – 43.4	Yes – 62.3%, No-37.7%	Prospective, randomized, phase III, double-blind	79%	13.7	14.5	N/A

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Nicholas J. Robert et al., 2017 [25]	266	Herceptin (Roche)	57.3	Positive – 58.3%, negative – 41.7	N/A	Retrospective, observational	N/A	16.4	16.9	N/A
Sabino De Placido et al, 2018 [24]	155	Herceptin (Roche)	52	Positive - 70%, negative – 30%	Yes – 48%, No – 48%, missing 4%	Retrospective, observational	N/A	80	27.8	N/A
Alan Celik et al., 2022 [29]	117	Biosimilar trastuzumab, ontruzant (SB3)	60	Positive - 63%, negative – 37%	Yes – 55% No – 45%	Retrospective, observational	N/A	11.1	15.4	N/A
Our study	61	Biosimilar trastuzumab ABP 980,	54	Positive – 78.3% Negative - 27.1%	Yes -55.7% No – 44.3%	Retrospective, observational	68.9 %	36	18.0	N/A