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ORIGINAL ARTICLE

Pertuzumab, trastuzumab and taxane-based treatment for visceral organ metastatic, trastuzumab-naïve breast cancer: real-life practice outcomes

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Abstract

Purpose In this study, we aimed to describe the real-life practice outcomes of pertuzumab–trastuzumab–taxane (PTT) combination in visceral organ metastatic, trastuzumab-naive breast cancer (BC) patients.

Methods This study was conducted by Turkish Oncology Group and included 317 patients' data from 36 centers.

Results Median age was 51 (22–82). Median PFS was 28.5 months, while median OS was 40.3 months. Patients with brain metastases (*n*: 13, 4.1%) had worse PFS (16.8 m vs. 28.5 m; $p=0.002$) and OS (26.7 m vs. 40.3 m; $p=0.009$). Patients older than 65 years of age (*n*: 42, 13.2%) had significantly lower OS results (19.8 m vs. 40.3 m; $p=0.01$). Two hundred sixty-eight patients (86.7%) received docetaxel while 37 patients (11.7%) received paclitaxel. PFS and OS were similar between taxane groups. In eight patients (2.5%), 5–40% ejection fraction decrement from baseline was detected without any clinical sign of heart failure.

Conclusions Our RLP trial included only visceral metastatic, trastuzumab-naïve BC patients including cases with brain involvement who received PTT combination in the first-line treatment. Regardless of negative prognostic characteristics, our results are in parallel with pivotal trial. Further strategies for brain metastasis should be developed to improve outcomes despite encouraging results with PTT treatment. Taxane selection can be personalized and endocrine maintenance may further improve outcomes after taxanes were discontinued. To our knowledge, this is the largest scale real-life clinical practice study of pertuzumab–trastuzumab–taxane therapy to date.

Keywords Pertuzumab · Trastuzumab · AntiHER2 · Visceral metastasis · Brain metastasis

Introduction

Metastatic disease accounts for 6–10% of newly diagnosed breast cancer cases [1] and 20–30% of all BC patients will have metastasis during the course of the disease [2]. HER2-positive BC subtype constitutes 15–20% of all BC, has an aggressive course, used to have a dismal prognosis [3, 4]. Anti-HER2 agents are a milestone in the treatment of HER2-positive breast cancer [5–8].

Trastuzumab is a monoclonal antibody developed against the extracellular component of HER2 and inhibits homodimerization via binding to subdomain IV of HER2 receptor. Trastuzumab is the first targeted therapy and is part of standard care for HER2-enriched BC patients. Pertuzumab is a similar monoclonal antibody that binds to the subdomain II of HER and additionally inhibits heterodimerization between HER2 receptors.

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In the pivotal phase III CLEOPATRA trial which enrolled 808 patients, pertuzumab–trastuzumab–docetaxel combination demonstrated an improvement in progression-free survival (PFS, median 19 vs. 12 months) and overall survival (OS, median 56.5 vs. 40.8 months). Pertuzumab, trastuzumab and docetaxel combination in first-line treatment of metastatic BC was approved following the CLEOPATRA trial.

Clinical trials may have rigorous exclusion criteria, which may lead to a patient cohort not precisely reflecting real-life practice (RLP). On the other hand, in RLP studies, a more diverse group of patients were represented in terms of patients' clinical status, performance, and comorbidities. Therefore, clinical effectiveness or toxicity profile may not be different compared to clinical trials.

In this study, we aimed to investigate retrospectively, clinical outcomes of the pertuzumab, trastuzumab, taxane (PTT) combination in first-line treatment of 317 trastuzumab-naïve, visceral organ metastatic BC patients, from 36 centres.

Materials and methods

This study was conducted by Turkish Oncology Group (TOG) and reached 36 centres. Visceral organ metastatic, trastuzumab-naïve, HER2-positive 317 BC patients who received PTT combination in first-line treatment were included retrospectively.

Patients who were diagnosed with metastatic HER2-positive BC (per ASCO/CAP guidelines) who have not received trastuzumab and have visceral organ metastasis beyond skeletal and lymph node involvement, were included retrospectively. Patients' clinical, demographical and histopathological characteristics, the number of courses and doses of taxane and pertuzumab–trastuzumab, adverse events, dose changes, reasons for treatment change and types of second-line treatments were recorded.

Laboratory and imaging test results were individually obtained from the electronic registration systems of the participating cancer centres. Visceral metastasis was accepted as target or non-target lesion in liver, lung, brain or any additional visceral organs. Only lymph node metastatic patients or presence of only skeletal metastasis were not accepted. Hormone receptor expression was considered positive in case of oestrogen receptor (ER) and/or progesterone receptor (PgR) immunostaining greater than 1% of invasive cells. HER2 status was evaluated by immunohistochemistry and level 3 expression was accepted as positive. In case of level 2 postivity, fluorescence in situ hybridization (FISH) or silver in situ hybridization (SISH) was performed.

Response rates were assessed according to RECIST 1.1 criteria and were collected in central database [9]. Because the centres were so widely distributed, central analyses of images could not be conducted.

In all of the centres, PTT combination was administered once every 3 weeks and was continued until progression or unacceptable toxicity. Treatment was also discontinued if the patient refused the treatment. Paclitaxel was administered (80 mg/m^2) weekly and docetaxel (75–100 mg/m^2) was administered once in 21 days. Trastuzumab was administered at a dose of 8 mg/kg for loading followed by 6 mg/kg and pertuzumab was administered with a bolus dose of 840 mg followed by 420 mg once every 21 days. The application of PTT combination in two consecutive days vs. on a single day was optional.

Cardiac monitorization was done by transthoracic echocardiography with left ventricular ejection fraction (LVEF) measurements as a routine in baseline and every 2–3 months during the follow-up periods. Any change in LVEF was recorded by the centres. If LVEF decreased below 45% or an absolute ≥ 10 decrease happened below baseline, treatment was withheld. Any symptomatic heart failure was an indication of treatment discontinuation.

The beginning of the PTT administration was accepted as the index date and all calculations were made accordingly. The PFS was calculated as the duration from the index date until the event of first progression or death. The OS was defined as the duration between the index date and the time of exitus report or lost to follow-up. Treatment toxicity was defined and graded according to common terminology criteria for adverse events guidelines (CTCAE v4.3) [10]. Adverse events recordings were made between the index date and 30 days after the last dose of pertuzumab. Patients who received at least one course of pertuzumab were included for safety analysis. For calculation of survival endpoints, at least three courses of treatment (one interval response assessment) were mandatory.

The study was approved by the committee of University of Health Sciences, Ankara Oncology Education and Research Hospital (TUEK meeting number: 40-15.5.2018). Given the retrospective nature of the study, written informed consent was not mandatory according to local regulations.

Data were analysed using the IBM Statistical Package for Social Sciences (SPSS®) v.21 (IBM Inc.; Armonk, NY, USA). Safety margin was accepted as 95% throughout the study. Kaplan–Meier method was employed for survival analysis, log-rank test for comparison in subgroups, and Cox-regression model for multivariate analysis.

Results

The real-life PTT treatment population from 36 cancer centres consisted of 317 patients with metastatic BC. Median age was 51 (22–82), and 42 patients were older than 65 years

Table 1 Patient characteristics

	N = 317	%
Median age (year, range)	51 (22–82)	
> 65 years-old patients	42	13.2
Hormone receptor status		
ER and/or PgR-positive	186	58.7
ER/PR-negative	130	41.1
Unknown	1	0.1
Histological subgroup		
Invasive ductal carcinoma	298	94.0
Invasive lobular carcinoma	3	0.9
Mixed	5	1.6
Others	11	3.5
HER2 status		
IHK 3+	267	84.2
IHK 2+/FISH positive	29	9.1
IHK 2+/ SISH positive	21	6.6
Prior therapies		
De-novo metastatic patients	282	89.0
Prior antracyclines	24	7.6
Prior trastuzumab	NA	NA
Metastatic site distribution		
Liver ± LN/skeletal	121	38.2
Lung ± LN/skeletal	151	47.6
Brain + liver/lung	7	2.2
Brain only	6	1.9
Liver + lung	23	7.3
Other	9	2.8
Only skeletal or only LN	NA	NA

ER oestrogen receptor, *Pgr* progesterone receptor, *LN* lymph node, *NA* not available, *FISH* fluorescence in situ hybridization, *SISH* silver in situ hybridization

at diagnosis (13.2%). All patients were trastuzumab-naïve, 89% were de-novo metastatic and 7.6% received anthracyclines in adjuvant setting. Among the patient population, 34 of them were initially presented as early stage breast cancer (24 patients as stage III and 10 patients as stage II), they developed visceral metastasis later following adjuvant treatment. Patient characteristics are shown in Table 1. Of patients, 58.7% were HR-positive, 84.2% were level-3 HER2 positive. In situ hybridization methods confirmed 15.7% patients as HER2-positive. Having brain metastasis was an exclusion criterion for the CLEOPATRA trial (Table 2). On the contrary, in our RLP, 13 of 317 (4.1%) patients had brain involvement at baseline staging images.

The median number of pertuzumab–trastuzumab cycles and docetaxel was 10 (1–75) and 6 (1–23), respectively. The median duration of pertuzumab–trastuzumab therapy was 7.5 months (0.75–56.3). Paclitaxel was the choice of taxane in 37 patients (11.7%) with a median 15 weeks (6–78 weeks) duration. Endocrine therapy (ET) was not allowed after omitting taxanes in the CLEOPATRA trial [11]. As a difference from pivotal study, maintenance ET was used for 94 patients in RLP (55.3% of HR-positive cases). Of note, 80 HR-positive patients did not receive ET after taxane was discontinued (44.1% of the HR-positive patients).

Details of treatment schedules and dose reductions are shown in Table 3. In two cases, paclitaxel dose was reduced due to worsening in performance status and in one case due to neuropathy. Docetaxel dose was reduced in 37 patients (13.2% of docetaxel population). Consistent or grade 3–4 neutropenia was the most common reason for docetaxel dose reduction.

On the cut-off date for data collection (25.2.2018), median follow-up time was 11.8 months (range 3.4–60.1 months). 60 disease progressions were noted. The median PFS was calculated as 28.5 months (95% CI 15.6–41.4,

Table 2 A brief comparison of patient characteristics between RLP and CLEOPATRA trial

Characteristics of patients (RLP vs. CLEOPATRA trial)	Real-life practice	CLEOPATRA trial[12]
Median age (range)	48 (22–82)	54 (22–82)
	N = 317 (%)	*N* = 402 (%)
> 65 years of age	43 (13.6)	NR
Receptor status		
ER and/or PgR positive	186 (58.7)	189 (47)
ER/PgR negative	130 (41)	212 (53)
Unknown	1	1
Prior treatments		
Anthracycline	74 (23.3)	150 (37.3)
Trastuzumab	None	47 (11.7)
Metastatic sites		
Brain	13 (4.1)	None
Non-visceral (isolated bone or LN)	None	88 (21.9)

RLP real-life practice, *ER* oestrogen receptor, *PgR* progesterone receptor, *LN* lymph node

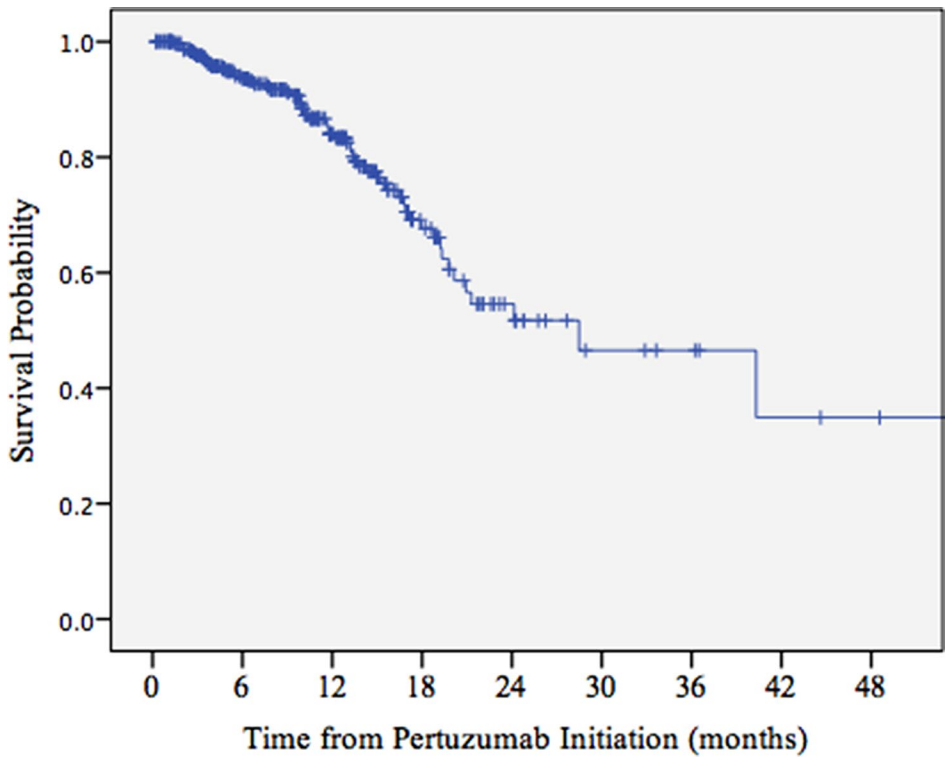
Table 3 Treatment characteristics and dose modifications

Treatment characteristics	Patients treated		Number of cycles				
	n	%	Median		Range		
Pertuzumab–trastuzumab	317	100	10		1–75		
Docetaxel	280	88.3	6		1–23		
Paclitaxel (weekly)	37	11.7	5		2–26		
Dose reductions	Dose reducted patients		Reasons (*n*)				
	n	%	NP	PS	*N*	*D*	CT
Pertuzumab–trastuzumab	2	4.8	–	–	–	–	2
Docetaxel	37	88.1	2	1	33	1	–
Paclitaxel (weekly)	3	7.1	1	2	–	–	–

RLP real-life practice, *ER* oestrogen receptor, *PgR* progesterone receptor, *LN* lymph node

Fig. 1). Hormone receptor positivity (ER and/or PR positive vs. ER-PR negative), de-novo metastatic status and the number of metastatic sites (less than 2 sites, 2–4 sites or more than 5 sites) did not affect the PFS results (Table 4). Patients with brain metastases had shorter PFS (16.7 months vs. NR; HR 2.67, 95% CI 1.3–5.4; $p = 0.004$, Table 4). Liver metastatic 129 patients had a median 28.4 months of PFS, and lung metastatic 159 patients had median 31.1 months of PFS. Patients with both liver and lung metastasis (dual visceral metastasis) had markedly worse outcome (PFS: 16.7 months, $p < 0.001$, Table 4). Liver metastatic patients had significantly better PFS rates compared lung metastatic cases and dual visceral organ metastatic patients ($p < 0.001$). Furthermore, having both lung and liver metastasis was found as a negative prognostic factor for PFS ($p < 0.001$, Fig. 2).

Fig. 1 Progression-free survival



Number of Patients	Number of PFS events	Median PFS (95% CI)	Mean PFS (SE)
317	60	28.4 (15.6-41.3)	31.6 (2.4)

Table 4 Subgroup PFS and OS analyses of real-life practice

Characteristic	Value (*n*/%)	PFS analyses				OS analyses			
		Survival (months)	*p*	HR	95% CI	Survival (months)	*p*	HR	95% CI
Age, year									
< 65 years	42 (13.2)	28.5	0.23	Ref.		NR	**0.007**	Ref.	
> 65 years	275 (86.8)	19.8		1.5	0.8–3.1	19.9		2.8	1.3–6.4
Brain metastasis									
Present	13 (4.1)	16.7	**0.004**	2.7	1.3–5.4	26.7	**0.007**	**3.2**	**1.3–7.7**
Absent	304 (95.9)	NR		Ref.		NR		Ref.	
Site of visceral organ metastasis									
Liver or lung only	281 (92.4)	28.3	**0.0001**	Ref.		NR	**0.0001**	Ref.	
Both liver and lung	23 (7.5)	16.7		3.6	1.8–7.1	18.7		4.7	2.1–10.4
Anti-hormonal maintenance									
No	89 (47.8)	20.9	**0.003**	Ref.		33.6	**0.01**	Ref.	
Yes	97 (52.2)	NR		0.3	0.2–0.7	NR		0.3	0.1–0.8
Docetaxel treatment									
< 6 cycles	84 (29.7)	21.3	**0.001**	4.1	1.7–9.6	26.7	**0.0001**	14	3.1–62.4
6 cycles	73 (25.9)	NR		Ref.		NR		Ref.	
> 6 cycles	125 (44.3)	28.4		1.2	0.5–2.8	40.2		3.5	0.8–15.2

Not all case data are available

Statistically significant values are in bold

PFS progression-free survival, *OS* overall survival, *NR* not reached, *CI* confidence interval, *HR* hazard ratio

A total of 33 patients (10.4%) died while on treatment. One patient died due to acute ischemic cardiac event which was not related to chemotherapy. One patient died due to infectious complication of femur prosthesis. In rest of 31 patients, cancer-related mortality has happened. Only one patient withdrew her chemotherapy consent and did not continue cancer treatment again.

The median OS was calculated as 40.3 months (95% CI 26.8–53.7, Fig. 3). Similar to PFS, OS results were not affected by de-novo metastatic status or the number of metastatic sites. On the other hand, a trend, although not statistically significant, was noted between HR positivity and longer OS (NR vs. 40.3 months, $p = 0.058$, Fig. 5). In term of OS rates, metastatic pattern was of significance. Median OS rates for liver or lung metastatic patients was not reached. On the other hand, median OS duration of dual metastatic patients was recorded as 33.6 months. Visceral organ metastasis type did a difference in OS rates. It is estimated that lung metastatic patients and liver metastatic patients will have longer median OS rates compared to dual metastatic patients ($p < 0.001$, Fig. 4). Brain metastasis was found to be associated with lower OS (26.7 months vs. NR; HR 3.2, 95% CI 1.3–7.7; $p = 0.007$).

In the first response assessment ($n = 275$); complete response (CR) was observed in 11 cases (4%), at least partial response (PR) was observed in 241 cases (87.7%) and 16 patients (5.8%) had stable disease (SD). In seven of the patients (2.5%), progression was noted in the first response assessment. Accordingly, the clinical benefit rate (CBR = CR + PR + SD) after 3 months of treatment was 97.5%. Among the patients who completed 6 months of treatment ($n = 232$), CBR was 97%.

Of the 317 patients, 286 of them (90.2%) experienced at least one side effect. A summary of the adverse events is presented in Table 5. Grade 3–4 toxicity was observed in 66 cases (31.2%), and neutropenia was found to be the most common grade 3–4 toxicity ($n = 57$, 17.9%). One treatment-related toxic death was recorded. The patient died due to febrile neutropenia and septic shock after fourth cycle of PTT.

None of the patients had a LVEF < 55% before starting PTT combination. In eight patients (2.5%), LVEF decrement from baseline occurred during treatment. In two patients, a 40% decrease was observed, and there was no clinical sign of heart failure. In those patients, treatment was discontinued permanently and no improvement was observed in LVEF until the data collection cut-off. In four patients, the rate of LVEF decrease from baseline was 25%, 20%, 15%, and 11%. Upon discontinuation of the therapy in the first two patients (with decrease rates 25% and 20%); LVEF returned to basal level, but PTT therapy was not started again. The last two patients (with decrease rates 15% and 11%) with LVEF decrease continued to receive PTT without any further decrease but more with careful follow-up in every cycle. In two patients, LVEF decrease rate was below 5%,

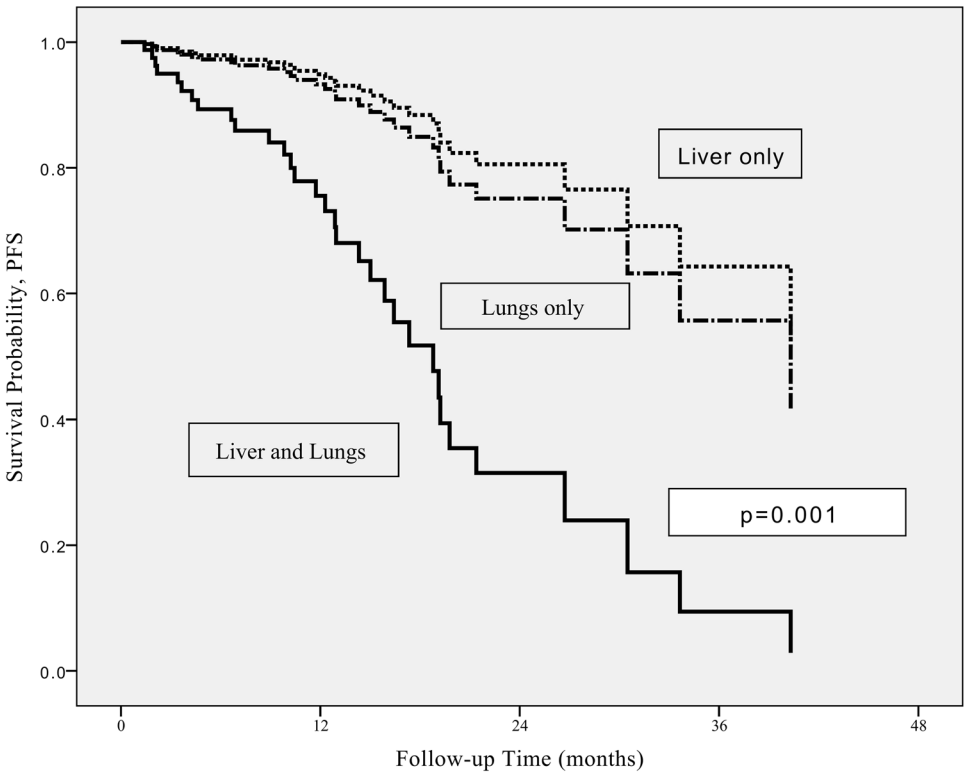


Fig. 2 Progression-free survival differences according to metastatic sites

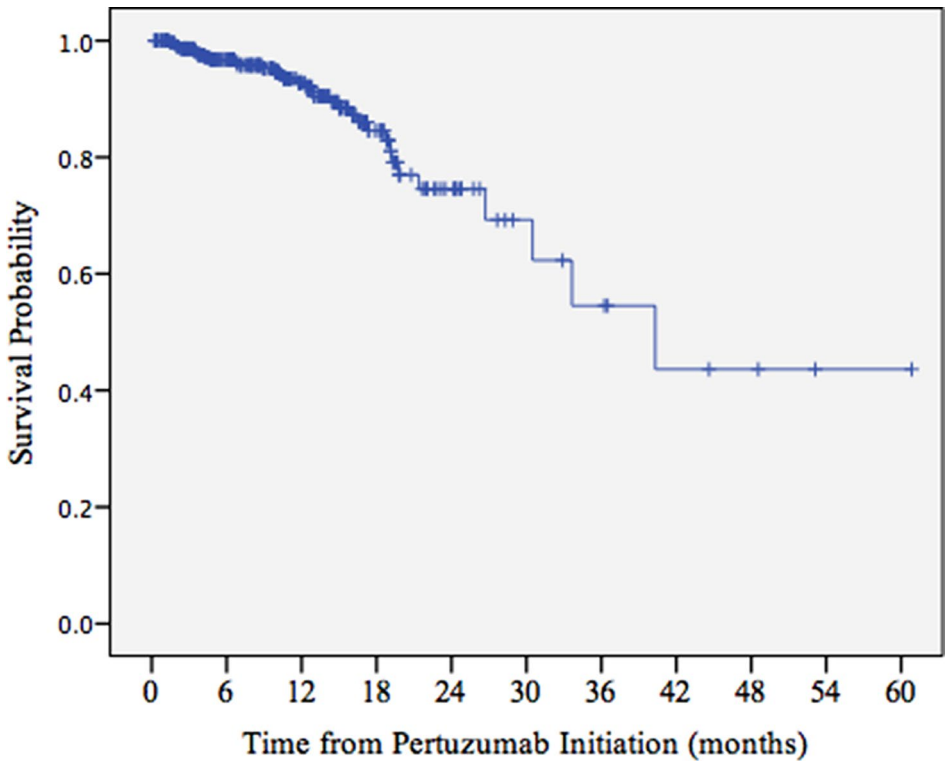


Fig. 3 Overall survival

Number of Patients	Number of OS events	Median OS (95% CI)	Mean OS (SE)
317	33	40.3 (26.8-53.7)	40.7 (3.6)

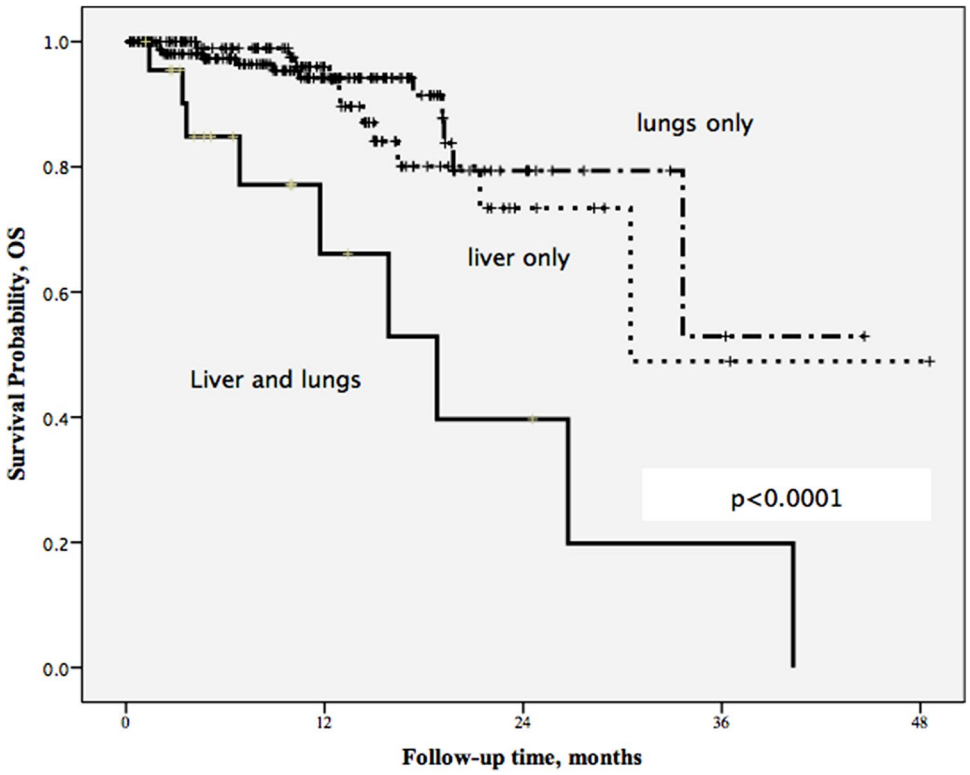


Fig. 4 Overall survival differences according to metastatic sites

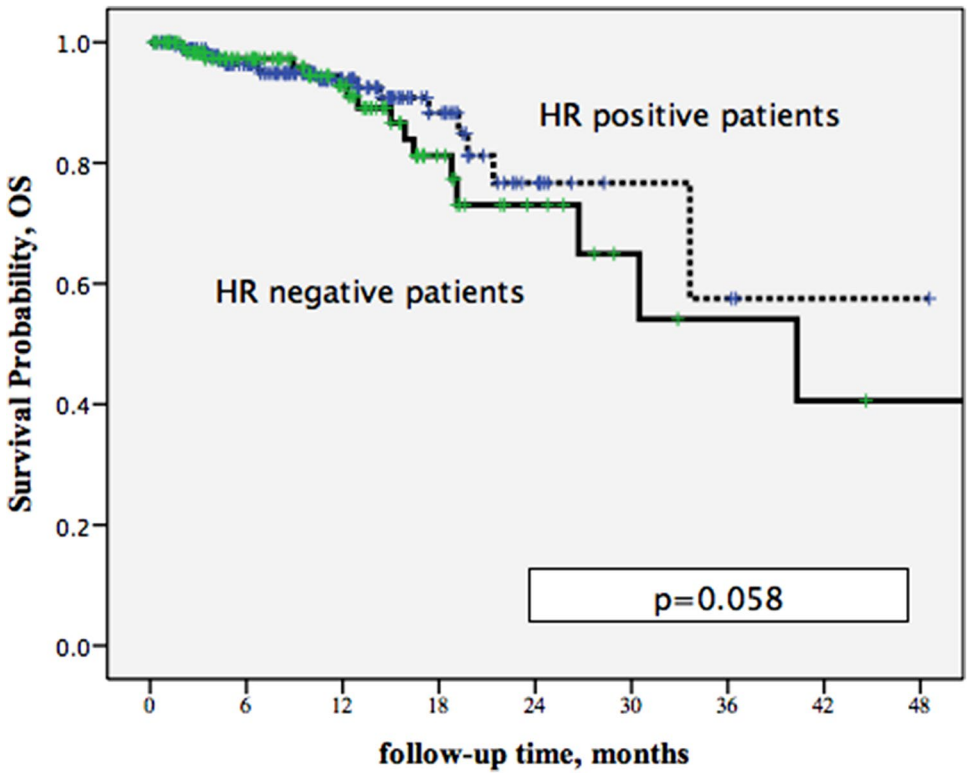


Fig. 5 Overall survival differences according to hormone receptor status

Table 5 Reported adverse events in real-life practice ($n=317$)

	Grade 1–2 *N* (%)	Grade 3–4 *N* (%)	Total *N* (%)
Fatigue	197 (62.1)	5 (7.9)	222 (70)
Emesis	127 (40.1)	–	127 (40.1)
Transfusion reaction	25 (7.9)	–	25 (7.9)
Rash	32 (10.1)	2 (0.6)	34 (10.7)
Mucositis	60 (18.9)	2 (0.7)	62 (19.6)
Myalgia	101(31.9)	–	101 (31.9)
Arthralgia	74 (23.3)		74 (23.3)
Neutropenia	58 (18.3)	57 (17.4)	113 (35.7)
FEN	–	13 (4.1)	13 (4.1)
Diarrhoea	67 (21.1)	11 (3.5)	78 (24.6)
Thrombocytopenia	22 (6.9)	3 (0.9)	25 (7.8)
Increase in transaminases	27 (8.5)	2 (0.6)	29 (9.1)
Hyperbilirubinemia	6 (1.9)	–	6 (1.9)
Peripheral neuropathy	58 (18.3)	2 (0.6)	60 (18.9)
Hypokalemia	9 (2.8)	–	9 (2.8)
LVEF decrement	6 (1.9)	2 (0.6)	8 (2.5)

NP neuropathy, *PS* ECOG PS decrement, *N* neutropenia, *D* diarrhoea, *CT* cardiac toxicity

therefore no change in treatment was necessary and no further decrease was observed.

In terms of constitutional symptoms, 70% of patients had fatigue, 10.7% of the cases had rashes and 7.9% had transfusion reaction. Forty percent of the patients had nausea in grade 1 or 2, despite antiemetic prophylaxis being performed routinely. Sixty patients (18.9%) had neuropathy.

Discussion

Visceral metastatic HER2-positive BC has a dismal prognosis. Combined treatment of pertuzumab–trastuzumab with docetaxel achieved a milestone in pivotal phase III trial [12]. However, in CLEOPATRA trial, the patient population was heterogenous including only lymph node or bone metastatic cases without any visceral organ involvement (22% of study population). Furthermore, brain metastasis was an exclusion criterion. The current study is the report of real-life PTT treatment in 317 trastuzumab-naïve, HER2-positive mBC patients with only visceral organ metastasis, including cases with brain involvement.

In our RLP setting, despite the overall poor prognostic characteristics (visceral organ metastatic patients beyond skeletal and lymph node involvement and also brain metastatic cases), median PFS was 28.5 months (mean PFS 31.6 months, see Fig. 1); longer compared to CLEOPATRA trial (18.5 months) [12]. Of note, in trastuzumab-naïve subgroup, PFS in the triple combination arm was 26.5 months. Previously reported Italian real-life practice study enrolled 150 metastatic BC patients which include both trastuzumab-naïve and prior trastuzumab exposed cases; brain metastasis was present in 6% of population and half of the patients had been diagnosed with non-visceral and bone-only metastatic disease [13]. Despite these differences between Italian RLP patients and our cohort, PFS results were similar (27.8 m vs. 28.5 m).

Clinical features of our patient cohort may have influenced the PFS results. Firstly, compared to CLEOPATRA (47%) our population includes more HR-positive cases (68.1%) which may act as a positive prognostic factor (Table 2). However, HR status was not found to be statistically significant in univariate analyses. Second, maintenance ET may have had an influence on PFS differences, and our RLP included hormonal maintenance after omitting taxanes. A bias due to unequal response assessment criteria and timing across centres could have happened. However, this negative impact might be less concerned because participating centres assessed response and/or progression according to RECIST 1.1 criteria and assessments every 3–4 cycle assessment were done routinely. Our patients were all trastuzumab-naïve. Previously, it had been shown that patients who were trastuzumab-naïve have superior outcomes to those that had undergone trastuzumab in adjuvant/neoadjuvant setting [14]. Hence, for our patients, lack of trastuzumab exposure in prior treatment history may have contributed to better PFS results. Finally, another confounding factor might be the metastatic status of patients. In our RLP population, due to reimbursement regulations, only visceral metastatic patients were represented. This could have been expected to result in earlier progressions in patients. The broad definition of visceral organ metastasis, may have led to a potential

discrepancy in the total metastatic tumour volume of patients among participating cancer centres and thus higher than expected PFS. The lower PFS result of multiple organ metastatic patients supports this hypothesis.

Brain metastasis is one of the negative prognostic factors for HER2-positive BC and is usually an exclusion criterion in phase III studies. Hence, the benefits of anti-HER2 treatments are not adequately reflected for brain involvement. On the other hand, our RLP data involve 13 (4.1%) brain metastatic patients, whose PFS rate was recorded as 16.7 months and OS rate as 26.7 months, respectively (Table 4). Our results support the efficacy of PTT combination in brain metastasis. On the other hand, brain involvement is the worst prognostic factor among other visceral organs with PTT treatment. Hence, in HER2-positive brain metastatic breast cancer patients, there is still an unmet need for effective treatment strategies.

A limitation of most phase III clinical studies, including the CLEOPATRA trial, is the underrepresentation of elderly population. Older age may be an exclusion criterion due to comorbidities, performance status and the risk of polypharmacy. On the contrary, in this RLP cohort, 42 patients (13.2%) were over 65 at initial diagnosis, and 8 patients were over 75 (Table 2). Using univariate analysis, a trend in lower PFS was found for patients who were over 65, but this difference was not statistically significant (19.8 vs. 28.5 months, $p = 0.23$; HR 1.5, 95% CI 0.8–3.1, Table 4). Of note, while the PFS rate was lower for older patients, it was still concordant with the subgroup analysis of CLEOPATRA study [15]. In the PERTAIN trial, P–T combination without taxanes rather than metronomic cyclophosphamide was tested for frail, older patients [16]. The authors reported that this combination can lengthen the PFS by 7 months (12.7 vs. 5.6 months, $p =$ NS) and delay or omit the need for taxanes. Hence, our results can serve as a sign of potential benefit for older patients with PTT combination, although there are still unanswered questions regarding optimal combination of dual-HER2 agents with cytotoxics or hormonotherapy for this special population.

To date, no optimal cytotoxic agent has been identified as first-line treatment for HER2-positive mBC. Initially, docetaxel was used and PTT was licensed by authorities [17, 18]. Median docetaxel cycle was 8 (1–35) and median study-treatment cycle was 18 (1–52) in the CLEOPATRA trial, respectively. In our RLP cohort, patients' median docetaxel cycle was 6 (1–23) and median P–T cycle was 10 (1–75). In addition, 37 patients (11.7%) were treated with paclitaxel. An interim analysis of ongoing Per-Use trial showed the safety of paclitaxel and nab-paclitaxel in combination with pertuzumab–trastuzumab [19, 20]. In univariate analyses, Similar to PERUSE study, PFS did not differ between docetaxel and paclitaxel groups in our patient population ($p = 0.67$). In RLP; paclitaxel was an option for clinicians for use in case of allergic reaction, intolerance and specific toxicity of docetaxel. Hence, in conjunction with Per-Use preliminary analysis and phase II studies, our results support the efficacy of paclitaxel for combination [21, 22]. The taxane option may be an alternative according to patient profile, comorbidities and expected adverse events without any compromise in survival outcomes which remains to be elucidated further in comparative analyses.

Optimal dose of chemotherapy has been another concern in practice. Main toxicities of PTT combination were observed during taxane infusions and the optimal dose that maximizes benefits while avoiding adverse events are not very well established. In CLEOPATRA study, a minimum of six cycles of docetaxel was recommended, while more than six cycles is optional for primary treating physicians [12]. A recent post-hoc analysis of CLEOPATRA trial showed that more than six cycles of docetaxel administration was not associated with better PFS results. On the other hand, less than six cycles of administration was linked to poorer prognosis [23]. According to Cox proportional hazards model, the present study has OS and PFS similar to pivotal trial. The patients who derive the most benefit from PTT combination received at least six cycles of docetaxel (Table 4). In the absence of evidence regarding significant benefit with more than six cycles of docetaxel, discontinuation of chemotherapy backbone is reasonable without any detrimental effect on survival. On the other hand, it is ideal to avoid administering cytotoxic chemotherapy in lower cumulative doses.

ET maintenance is a unique feature of our study that differentiates it from the CLEOPATRA trial. Among 186 HR-positive patients, 52.2% of them received ET after taxane discontinuation. Per univariate analyses, ET maintenance created a significant PFS and OS difference (Table 4; Fig. 6). PERTAIN is a phase II study, in which P–T in combination with aromatase inhibitor (AI) was tested against T–AI combination. The preliminary results of PERTAIN study showed that addition of pertuzumab can be more beneficial for the patients [24]. Given the prolonged PFS and OS results of RLP, our study, in conjunction with the PERTAIN study may address ET maintenance after discontinuation of chemotherapy backbone.

The adverse event reports (AE) collected during clinical study period are limited to selected patient group and sample size. As the drug becomes more available for patients, side effects may become more apparent [25]. Therefore, in real-life there is a critical need for assessing toxicity beyond determining efficacy. In this patient cohort, main toxicities are grade 1–2 fatigue (70%) and neutropenia (35.6%). Grade 3–4 adverse events were observed in 69 patients (21.8%) of which leukopenia, mucositis and diarrhoea are the most common ones (Table 5). Notably, no unexpected AE was observed. One toxic death due to febrile neutropenia and

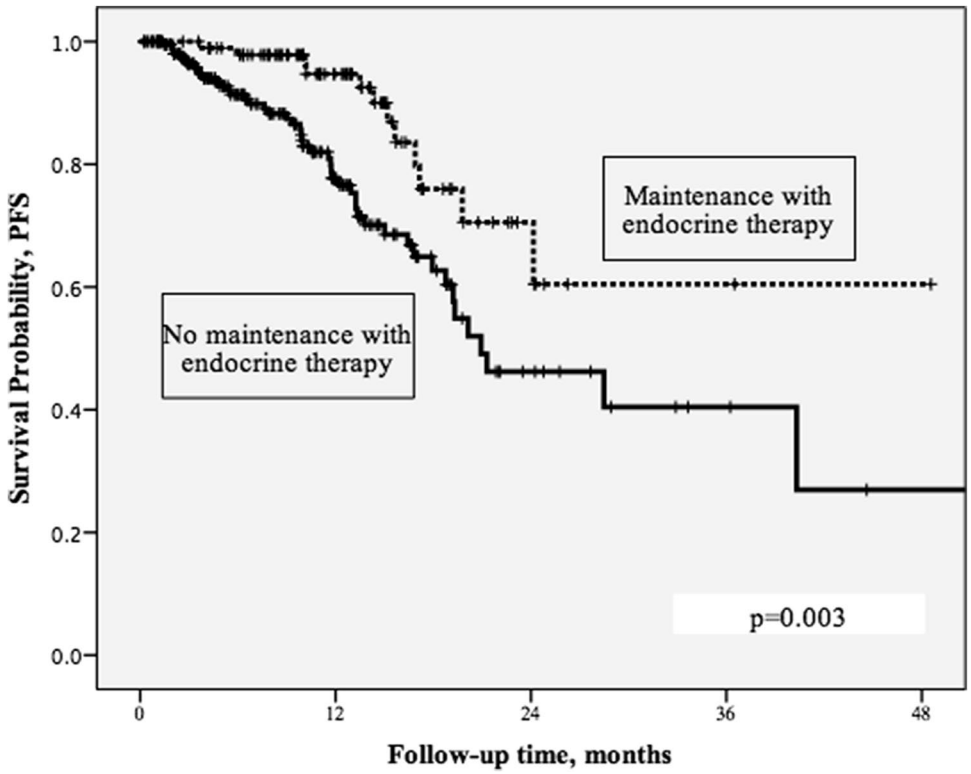


Fig. 6 Progression-free survival differences according to endocrine therapy maintenance status

septic shock was recorded. Cardiac toxicity rate was similar to pivotal study and no clinical sign of heart failure was observed. In a recent RLP analysis, the rate of EF decline was noted in 13% of cases, > 20% decrease was reported in 4.5% of patients [26]. Our results are more encouraging in a larger cohort of patients.

Our RLP study is subject to inherent limitations. Multicentricity allows for a diverse patient population; however, it also leads to variance in the timing and interpretations of assessments across centres [27]. This study utilized medical recordings and clinical notes that may contain missing or inaccurate data. Retrospective, observational studies are generally biased in terms of reporting toxicities. However, the national regulatory authority mandates reporting of adverse events according to pharmacovigilance guidelines. Hence; the retrospective, observational design of our study is less likely to have a negative impact on the rate of reported toxicities.

In conclusion, our RLP trial included only visceral metastatic, trastuzumab-naïve mBC patients including brain metastatic cases who received PTT combination in the first-line treatment. Regardless of negative prognostic characteristics, our results are in parallel with pivotal trial. Despite encouraging results with PTT treatment, further strategies for brain metastasis should be developed to improve outcomes despite encouraging results with PTT treatment. Moreover, according to our results, taxane selection might be personalized according to patient status and endocrine maintenance may further improve outcomes after taxanes were discontinued. To our knowledge, this is the largest scale real-life clinical practice study of pertuzumab–trastuzumab–taxane therapy to date.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

Ethics approval and consent to participate All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee

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