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Real-World Outcomes of Subcutaneous PHESGO® in HER2-Positive Breast Cancer: Pathological Response, Sequencing, and Safety

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Simple Summary

Breast cancer with human epidermal growth factor receptor 2 (HER2) positivity is aggressive but responds well to targeted therapy. PHESGO®, a subcutaneous fixed-dose combination of pertuzumab and trastuzumab, can be administered within minutes, reducing treatment time and hospital burden compared with intravenous infusion. We retrospectively analyzed 47 Japanese patients with HER2-positive breast cancer who received PHESGO® in neoadjuvant, adjuvant, or metastatic settings. In the neoadjuvant group, 65% achieved pathological complete response (pCR), similar to results from pivotal trials. Sequencing analysis showed that starting PHESGO® before anthracycline chemotherapy significantly improved pCR rates. In contrast, biomarkers such as Ki-67, hormone receptor status, and p53 did not predict response. Treatment was generally well tolerated, with mostly mild side effects and no symptomatic cardiac dysfunction, even in elderly patients. In metastatic cases, outcomes were consistent with intravenous standards. These findings highlight PHESGO® as a convenient, effective, and time-saving option in real-world practice.

Abstract

Background: Subcutaneous pertuzumab and trastuzumab with hyaluronidase (PHESGO®) provides a convenient alternative to intravenous dual HER2 blockade, offering markedly shorter administration time. However, real-world evidence in Asian populations remains limited. **Methods:** We retrospectively analyzed 47 Asian patients with HER2-positive breast cancer treated with PHESGO® between January 2024 and July 2025 across neoadjuvant, adjuvant, and metastatic settings. The primary endpoint was pathological complete response (pCR) in neoadjuvant cases. Secondary endpoints included biomarker associations, treatment sequencing, safety, and metastatic efficacy. **Results:** Median age was 65 years (range, 43–93). In the neoadjuvant group (n = 26), 17 patients (65%) achieved pCR. Sequencing analysis demonstrated higher pCR with PHESGO®-first regimens (85.7%) compared with chemotherapy-first regimens (41.7%, p = 0.038), suggesting benefit from early HER2 blockade. Biomarker analyses, including Ki-67, ER, PgR, and p53, showed no significant association with pCR. Treatment was well tolerated; the most common adverse events were dysgeusia (57%), diarrhea (38%), and rash (34%), almost all grade 1–2. Only one grade ≥3 event (thrombocytopenia) occurred, and no symptomatic cardiac dysfunction was observed. Safety profiles were comparable across age groups, though anemia was more frequent in elderly patients. In metastatic cases (n = 10), the objective response rate was 56% and disease control rate 78%, consistent with historical intravenous benchmarks. Importantly, the subcutaneous formulation allowed administration within minutes, substantially reducing treatment burden compared with intravenous infusion.

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Conclusions: PHESGO® demonstrated high efficacy, favorable tolerability, and practical advantages in daily practice. Its time-saving subcutaneous delivery and sequencing benefits support PHESGO® as an effective and convenient real-world option for HER2-positive breast cancer.

Keywords: subcutaneous administration; dual HER2 blockade; neoadjuvant chemotherapy; pathological complete response; treatment sequencing; real-world evidence

1. Introduction

Breast cancer continues to be the most common malignancy among women worldwide and remains one of the leading causes of cancer-related mortality. Despite improvements in screening, systemic therapy, and supportive care, the global burden remains high, with more than two million new cases annually and over half a million deaths reported each year. The disease is heterogeneous, and its clinical behavior and response to treatment are largely determined by molecular subtype. Among these, human epidermal growth factor receptor 2 (HER2)-positive breast cancer represents approximately 15–20% of cases. In the era before targeted therapies, HER2 positivity was associated with aggressive biology, early recurrence, and poor survival outcomes.

The development of HER2-directed therapy dramatically altered this natural history. The correlation between amplification of the HER2/neu oncogene and adverse outcomes was first described by Slamon and colleagues in 1987 [1], providing the biological rationale for targeted inhibition. The first successful targeted agent was trastuzumab, a monoclonal antibody directed against the extracellular domain IV of HER2. In a pivotal trial published in 2001, trastuzumab in combination with chemotherapy significantly prolonged survival in metastatic HER2-positive breast cancer [2], representing a paradigm shift in the management of this disease. Soon after, large randomized adjuvant trials, including HERA, NSABP B-31 and NCCTG N9831, confirmed the benefit of adding trastuzumab to standard chemotherapy for one year in early-stage HER2-positive breast cancer, reducing recurrence and mortality rates substantially [3,4].

The next major advancement came with pertuzumab, a monoclonal antibody that binds to the dimerization domain (subdomain II) of HER2, thereby preventing heterodimerization with HER3 and enhancing blockade of downstream signaling. The combination of trastuzumab and pertuzumab with docetaxel significantly improved survival in metastatic patients in the CLEOPATRA trial [5], which firmly established dual blockade as the preferred first-line regimen in advanced disease. In the neoadjuvant setting, the NeoSphere trial demonstrated that the addition of pertuzumab to trastuzumab and docetaxel increased the rate of pathological complete response (pCR) from 29% to 45.8% [6]. The TRYPHAENA trial further confirmed the efficacy of dual blockade with both anthracycline-containing and anthracycline-free chemotherapy regimens, showing high pCR rates and acceptable cardiac safety [7]. These data collectively transformed the standard of care, making dual HER2 blockade with trastuzumab and pertuzumab plus chemotherapy the cornerstone of treatment for HER2-positive breast cancer across stages.

Although trastuzumab and pertuzumab have revolutionized treatment, intravenous administration remains resource-intensive and burdensome. Infusion of trastuzumab and pertuzumab requires venous access, infusion chairs, pumps, and prolonged chair time for patients. Each administration may last hours, resulting in repeated lengthy hospital visits over the course of one year of adjuvant therapy. This is particularly challenging for elderly patients, those with poor venous access, and healthcare systems facing rising patient volumes. To overcome these limitations, a fixed-dose combination of pertuzumab and trastuzumab with recombinant human hyaluronidase was developed for subcutaneous injection. Commercially known as PHESGO®, this formulation enables delivery in minutes rather than hours, eliminating the need for infusion pumps and reducing the treatment burden for both patients and providers.

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The FeDeriCa phase III trial demonstrated that subcutaneous PHESGO® was pharmacokinetically non-inferior to the intravenous formulation and achieved nearly identical pCR rates in the neoadjuvant setting (59.7% versus 59.5%) [8]. The PHranceSCa trial further confirmed strong patient preference for the subcutaneous formulation, with most patients choosing to continue PHESGO® rather than return to intravenous treatment after experiencing both [9]. These findings underscored the potential of PHESGO® to streamline care without sacrificing efficacy or safety.

Nevertheless, real-world evidence regarding PHESGO® remains scarce. Clinical trials typically enroll highly selected patients, often younger and healthier than those seen in daily practice. In routine clinical settings, many patients are elderly, frail, or have comorbidities, making tolerability and feasibility particularly relevant. Moreover, the optimal sequencing of PHESGO® relative to chemotherapy remains unclear. Evidence from the TRAIN-2 and KRISTINE trials suggested that the order of HER2-targeted therapy and chemotherapy can influence outcomes, with early introduction of HER2 blockade potentially improving tumor eradication and reducing toxicity [10,11]. Biomarkers such as estrogen receptor (ER), progesterone receptor (PgR), the proliferation marker Ki-67 and tumor suppressor p53 and have been investigated in relation to pCR and prognosis in HER2-positive disease, but in PHESGO®, its relevance is unclear.

The objective of this study is to evaluate the clinical utility of PHESGO® in a real-world Japanese cohort. The objectives were to assess the rate of pCR in the neoadjuvant setting, to examine the influence of treatment sequencing on pCR, to explore biomarker associations with response, to characterize the safety and tolerability of PHESGO®, and to evaluate outcomes in metastatic patients. By integrating real-world outcomes with established clinical trial benchmarks, this study aimed to provide a comprehensive understanding of PHESGO® in daily practice.

2. Materials and Methods

This study was designed as a retrospective observational analysis at Nippon Medical School Tama-Nagayama Hospital, Tokyo, Japan. Consecutive patients with HER2-positive breast cancer who received at least one dose of PHESGO® between January 2024 and July 2025 were included. Clinical information was extracted from electronic medical records, pharmacy databases, and pathology reports. The study was approved by the institutional review board and conducted in accordance with the Declaration of Helsinki.

Patients were eligible if they had histologically confirmed invasive breast carcinoma and HER2-positive disease, defined as immunohistochemical (IHC) staining 3+ or 2+ with FISH (fluorescence in situ hybridization) amplification. Patients were included regardless of stage, provided they received PHESGO® in the neoadjuvant, adjuvant, or metastatic setting.

In the neoadjuvant setting, PHESGO® was administered with taxane-based chemotherapy, with or without anthracycline-based therapy sequentially. A standard regimen included docetaxel at 75 mg/m² every three weeks combined with PHESGO® on the same schedule. For anthracycline-based regimens, epirubicin 90 mg/m² plus cyclophosphamide 600 mg/m² were given every three weeks for four cycles, either before or after PHESGO® plus taxane. PHESGO® was given as a subcutaneous fixed-dose combination of pertuzumab 1200 mg, trastuzumab 600 mg, and hyaluronidase 30,000 units over approximately eight minutes for the loading dose, followed by pertuzumab 600 mg and trastuzumab 600 mg every three weeks delivered in about five minutes.

Sequencing was defined as PHESGO®-first (PHESGO® plus taxane followed by anthracyclines) or chemotherapy-first (anthracyclines followed by PHESGO® plus taxane) regimens. As with pegfilgrastim for the prevention of neutropenia, adjunctive therapy for complications was administered at the discretion of the physician.

In the neoadjuvant setting, patients who achieved pCR generally continued PHESGO® to complete one year of anti-HER2 therapy. Patients with residual invasive disease after neoadjuvant therapy were recommended trastuzumab emtansine (T-DM1) in line with the KATHERINE trial [12]. However, PHESGO® was continued in patients for whom T-DM1 was unsuitable due to age, comorbidity, or venous access issues. In cases treated with adjuvant therapy, regardless of the

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presence or absence of a 3-week anthracycline regimen (EC therapy x 4), a combination of taxane-based agents and PHESGO® was administered 4 times, followed by 14 doses of PHESGO® monotherapy, totaling 1 year of PHESGO® subcutaneous injections.

In the metastatic setting, PHESGO® was administered every three weeks, usually with docetaxel or paclitaxel, and continued until progression or unacceptable toxicity.

Pathological assessment was carried out by experienced breast pathologists. pCR was defined as ypT0/is ypN0, indicating no residual invasive cancer in the breast or axillary lymph nodes, with or without ductal carcinoma in situ. ER and PgR expression were evaluated by IHC, with nuclear staining in at least 10% of tumor cells considered positive. HER2 status was determined according to ASCO/CAP guidelines. Ki-67 was assessed as the percentage of positive tumor cell nuclei. p53 expression was classified as wild-type, mutant, or null, with mutant and null grouped together as positive.

The primary endpoint was the pCR rate in neoadjuvant patients. Secondary endpoints were biomarker associations with pCR, the impact of sequencing, the incidence and severity of adverse events graded by CTCAE v5.0, and treatment efficacy in metastatic patients according to RECIST v1.1.

Descriptive statistics were summarized baseline characteristics. Categorical variables were compared using Fisher's exact test. Odds ratios with 95% confidence intervals were calculated for biomarker associations, with 0.5 continuity correction for zero cells. Risk ratios and absolute differences were used for sequencing comparisons. Student's *t*-test was used to test for significant differences in mean values between the two groups, with $p < 0.05$ judged as statistically significant. Time-to-event analyses were not performed because of limited follow-up.

3. Results

3.1. Patient Characteristics (Table 1)

Between January 2024 and July 2025, a total of 47 patients with HER2-positive breast cancer were treated with PHESGO® at our institution. All patients were Asian women. As shown in Table 1, the median age was 65 years, ranging from 43 to 93 years. Among these patients, 23 (49%) were ER-positive, and 14 (30%) were PgR-positive, using the threshold of 10% nuclear staining. HER2 immunohistochemistry was 3+ in 36 patients (77%), while the remaining 11 patients (23%) were 2+ with confirmation of amplification by FISH. The median Ki-67 index was 45%, with a range from 10% to 95%, reflecting the high proliferative activity typical of HER2-positive tumors. Thirty-eight percent of tumors were classified as p53-positive, defined as either mutant overexpression or null staining patterns. Of the 47 patients, 26 were treated in the neoadjuvant setting, 11 received PHESGO® as adjuvant therapy after surgery, and 10 had metastatic disease.

Table 1. Patient Characteristics.

Characteristic	Overall (*n* = 47)	Neoadjuvant (*n* = 26)	Adjuvant (*n* = 11)	Metastatic (*n* = 10)
Age, median (range)	65 (43–93)	64 (45–83)	63 (43–86)	72 (55–93)
ER-positive (≥ 10%)	23/47 (48.9%)	11/26 (42.3%)	8/11 (72.7%)	4/10 (40.0%)
PgR-positive (≥10%)	14/47 (29.8%)	3/26 (11.5%)	7/11 (63.6%)	4/10 (40.0%)
HER2 IHC 3+	36/47 (76.6%)	22/26 (84.6%)	8/11 (72.7%)	6/10 (60.0%)
HER2 IHC 2+/FISH+	11/47 (23.4%)	4/26 (15.4%)	3/11 (27.3%)	4/10 (40.0%)
Ki67, median (range)	45 (10–95)	48 (20–90)	42 (10–80)	46 (20–95)
p53 mutant	18/47 (38.3%)	9/26 (34.6%)	5/11 (45.5%)	4/10 (40.0%)

3.2. Neoadjuvant Cohort and Pathological Complete Response

In the neoadjuvant cohort (*n* = 26), a total of 17 patients (65%) achieved pathological complete response (pCR). The pCR group demonstrated a mean Ki67 index of 47.7% (median 50%), whereas the non-pCR group had a mean Ki67 index of 51.6% (median 48%). Statistical comparison using the Mann–Whitney U test revealed no significant difference between the two groups ($U = 65.5$, $p = 0.73$). Similarly, other biomarkers showed no association with pCR. ER positivity was present in 59% of the

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pCR group versus 56% of the non-pCR group (p = 0.87). PgR positivity was 29% *vs.* 33% (p = 0.82). HER2 IHC 3+ tumors achieved pCR in 76% compared to 67%of the non-pCR group (p = 0.64). p53 positivity was observed in 35% of pCR and 33% of non-pCR patients (p = 0.91). No statistically significant differences were observed for any of these biomarkers between the pCR group and the non-pCR group.

Table 2. Relationship Between Preoperative Chemotherapy Efficacy and Biomarkers.

Variable	pCR Group (n = 17)	non-pCR Group (n = 9)	p-Value
Ki-67 (%)	47.7(mean50.0)	51.6%(mean51.6)	0.73
ER positive (%)	10 (59%)	5 (56%)	0.87
PgR positive (%)	5 (29%)	3 (33%)	0.82
HER2 IHC 3+ (%)	13 (76%)	6 (67%)	0.64
p53 mutant (%)	6 (35%)	3 (33%)	0.91

3.3. Impact of Regimen Sequence on pCR

In the neoadjuvant cohort (n = 26), patients were stratified according to regimen sequence. Those who received EC→PHESGO®+docetaxel (EC→DHP, n = 12) achieved a pCR rate of 41.7% (5/12; 95% CI, 19.3–68.0). By contrast, patients who received PHESGO®-based therapy prior to EC or noEC (PHESGO®-first: DHP→EC, HP + weekly Paclitaxel→HP, or DHP, n = 14) demonstrated a significantly higher pCR rate of 85.7% (12/14; 95% CI, 60.1–96.0). Weekly paclitaxel was administered to one elderly patient and was selected to avoid adverse events associated with docetaxel administered every three weeks. Statistical comparison using Fisher's exact test confirmed the difference as significant (p = 0.038). These findings suggest that introducing dual HER2 blockade with docetaxel prior to anthracycline may enhance the likelihood of achieving pCR. Although exploratory, these findings support the hypothesis that early introduction of HER2-targeted therapy enhances tumor eradication, echoing observations from the TRAIN-2 and KRISTINE trials [10,11].

3.4. Adverse Events

Treatment with PHESGO ®was generally well tolerated. As summarized in Table 3, the most frequent adverse events were taste disorder (57%), diarrhea (38%), rash (34%), nausea (32%), anemia (28%), neutropenia (26%), constipation 23%), stomatitis (23%) and leukopenia (21%). Importantly, nearly all events were grade 1 or 2. Only one patient (3.8%) aged 70 or older experienced a grade ≥3 event, which was thrombocytopenia. Anemia was more frequent in the elderly group (42% vs. 18%), but no statistically significant difference was observed(p = 0.068). Although there was a tendency for more people under 70 to have stomatitis (32% vs. 11%), this also did not show a significant difference(p = 0.086). No patients developed symptomatic left ventricular dysfunction, a major concern historically associated with trastuzumab-containing regimens [13,14]. Injection site reactions occurred in approximately 20% of patients but were mild and self-limiting. As shown in Table 3, adverse events were generally comparable between younger (<70 years) and older (≥70 years) patients., although severe toxicities and cardiac dysfunction were rare across both groups.

Table 3. Differences in Adverse Events (all grade) between those aged 70 and older and those younger than 70.

Adverse Event	All Patients(n = 47)	<70 yrs (n = 28)	≥70 yrs (n = 19)
Neutropenia	12(25.5%)	7/28 (25.0%)	5/19 (26.3%)
Leukopenia	10(21.2%)	5/28 (17.9%)	5/19 (26.3%)
Anemia (RBC* decrease)	13(27.7%)	5/28 (17.9%)	8/19 (42.1%)
Thrombocytopenia	1(2.1%)	0/28 (0.0%)	1/19 (5.3%)
Liver function disorder	4(8.5%)	2/28 (7.1%)	2/19 (10.5%)
Nausea	15(31.9%)	9/28 (32.1%)	6/19 (31.6%)
Vomiting	3(6.4%)	2/28 (7.1%)	1/19 (5.3%)

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Appetite loss	9(19.1%)	6/28 (21.4%)	3/19 (15.8%)
Constipation	11(23.4%)	7/28 (25.0%)	4/19 (21.1%)
Diarrhea	18(38.3%)	12/28 (42.9%)	6/19 (31.6%)
Pruritus	5(10.6%)	3/28 (10.7%)	2/19 (10.5%)
Epistaxis	3(6.4%)	2/28 (7.1%)	1/19 (5.3%)
Rash/Eczema	16(34.0%)	10/28 (35.7%)	6/19 (31.6%)
Dysgeusia (taste disorder)	27(57.4%)	17/28 (60.7%)	10/19 (52.6%)
Arthralgia	7(14.9%)	5/28 (17.9%)	2/19 (10.5%)
Fatigue	9(19.1%)	7/28 (25.0%)	2/19 (10.5%)
Stomatitis (oral mucositis)	11(23.4%)	9/28 (32.1%)	2/19 (10.5%)
Peripheral neuropathy	9(19.1%)	6/28 (21.4%)	3/19 (15.8%)
Lacrimation (watery eyes)	6(12.8%)	4/28 (14.3%)	2/19 (10.5%)
Edema	5(10.6%)	3/28 (10.7%)	2/19 (10.5%)
Heart failure	0(0.0%)	0/28 (0.0%)	0/19 (0.0%)

*RBC: Red Blood Cells.

3.5. Metastatic Outcomes

Ten patients received PHESGO® for metastatic HER2-positive breast cancer. All patients received chemotherapy for metastatic recurrent breast cancer as their initial treatment. This included three patients who switched from intravenous trastuzumab and pertuzumab therapy to PHESGO®. Nine patients were evaluable for response, five achieved partial response, two had stable disease and two experienced progression. This corresponded to an objective response rate of 56% and a disease control rate of 78%. These results are consistent with the efficacy of pertuzumab and trastuzumab plus docetaxel in the CLEOPATRA trial [5,15,16], supporting the use of PHESGO® in advanced disease as a convenient alternative to intravenous administration. Most adverse events were Grade 1–2, and no patients discontinued treatment due to adverse events. All three patients who had previously received trastuzumab and pertuzumab via intravenous infusion experienced shorter treatment times after switching to subcutaneous injection, and none requested a return to intravenous therapy.

4. Discussion

The present study represents one of the first real-world analyses of PHESGO® in Asian, providing valuable insights into its efficacy and safety across neoadjuvant, adjuvant, and metastatic settings. Several important observations emerge from our findings.

The pCR rate of 65% in the neoadjuvant cohort is consistent with pivotal trial results, including FeDeriCa, which reported nearly identical efficacy between subcutaneous (59.7%) and intravenous (59.5%) formulations [8]. In the NeoSphere trial, the group receiving docetaxel combined with both trastuzumab and pertuzumab demonstrated the highest pCR rate at 45.8%, compared to 29.0% for docetaxel plus trastuzumab and 24.0% for docetaxel plus pertuzumab [6]. Furthermore, the TRYPHAENA trial reported that adding dual HER2 blockade after anthracycline therapy did not significantly increase cardiotoxicity and achieved a high pCR rate (57.3 to 61.6%) [7]. Our study also demonstrated a 65% pCR rate with PHESGO®, confirming its efficacy as an alternative treatment to intravenous trastuzumab and pertuzumab.

Regarding the regimen sequence, despite some patients being on anthracycline-free regimens, sequencing analysis indicated that PHESGO®-first regimens yielded higher pCR rate than chemotherapy-first regimens (85.7% vs. 41.7%). Although based on small numbers, this observation supports the hypothesis that early introduction of HER2 blockade improves response. Furthermore, the combination of trastuzumab and pertuzumab may potentially eliminate the need for chemotherapy associated with adverse events. In TRAIN-2, which suggested that anthracycline-free regimens with early dual HER2 blockade (68%) were not inferior to anthracycline-containing regimens (67%) in pCR [10]. Meanwhile, the KRISTINE trial compared a group receiving docetaxel

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plus carboplatin with added trastuzumab and pertuzumab (TCHP) to a group receiving the antibody-drug conjugate trastuzumab emtansine plus pertuzumab (T-DM1+P). Grade 3 or higher adverse events were significantly lower in the T-DM1+P group (31% vs. 64%), while the pCR rate was significantly higher in the TCHP group (55.7% vs. 44.4%). Three-year event-free survival was also superior in the TCHP group (94.2% vs. 85.3%), suggesting limitations to omitting chemotherapy [11].

In this study, none of the biomarkers—including Ki67, ER, PgR, and p53—could be definitively shown to correlate with pCR. Ki67 is widely recognized as a marker of tumor proliferation and has been reported to correlate with chemotherapy sensitivity in breast cancer. Several studies and meta-analyses have suggested that tumors with higher Ki67 expression are more likely to achieve pCR following neoadjuvant treatment, particularly in HER2-positive and triple-negative subtypes [17–20]. Our study showed results that differed from these reports. However, the relationship is complex, as extremely high proliferation may also be associated with aggressive biology and risk of recurrence despite initial response. The lack of predictive value for ER and PgR is consistent with pooled analyses of HER2-positive disease, which indicate that hormone receptor positivity attenuates—but does not eliminate—the benefit of dual HER2 blockade [21,22]. The absence of association with p53 may reflect both biological heterogeneity and the limited sample size in our study.

Adverse events of PHESGO® were generally well tolerated, with no unexpected toxicities and only one case of grade ≥3 thrombocytopenia. The absence of symptomatic cardiac dysfunction is particularly reassuring, as cardiotoxicity has historically been a concern with trastuzumab-based regimens [13,14]. Importantly, when adverse events were stratified by age, safety profiles were largely similar between younger (<70 years) and older (≥70 years) patients. Notably, anemia occurred more frequently among elderly patients (42.1% vs. 17.9%), although this difference did not reach statistical significance ($p = 0.068$). This tendency is clinically meaningful, as older patients may have reduced bone marrow reserve and increased vulnerability to hematologic toxicity. Nevertheless, severe hematologic events were rare in both age groups, and cardiac dysfunction was not observed, indicating that PHESGO®-based therapy is broadly feasible even in the elderly population. The pain associated with PHESGO® subcutaneous injections was mild, and no patients requested discontinuation for this reason. These results are consistent with prior real-world observations that subcutaneous trastuzumab and pertuzumab combinations can be safely delivered in older patients without excessive toxicity [8,9].

Finally, metastatic outcomes with PHESGO® were comparable to those achieved with intravenous pertuzumab and trastuzumab, as demonstrated in CLEOPATRA [5,15,16]. In CLEOPATRA trial, compared to the docetaxel and trastuzumab group, the group receiving pertuzumab in addition to these agents showed a significant prolongation in progression-free survival (12.4 months vs. 18.5 months, HR 0.62, $p < 0.001$) and overall survival was also significantly prolonged (40.8 months vs. 56.5 months, HR 0.68, $p < 0.0001$). We also used PHESGO®, a subcutaneous injection, instead of intravenous administration of trastuzumab and pertuzumab in metastatic cases. Overall response rate (ORR, complete response and partial response) of 56% and disease control rate (DCR, stable disease and stable disease) of 78% are consistent with historical benchmarks, confirming that the subcutaneous route does not compromise efficacy in advanced disease.

This study has limitations. It was retrospective and conducted at a single institution, with a modest sample size and limited follow-up. Biomarker analyses were exploratory and not powered for definitive conclusions. Nonetheless, the consistency of our results with pivotal trials strengthens their external validity.

Looking forward, larger multicenter registries and prospective studies are warranted to validate these findings, particularly the impact of sequencing, biomarker associations, and age-specific tolerability. Integration of novel agents such as trastuzumab emtansine (T-DM1) [11,22,24] and trastuzumab deruxtecan [24,25] into treatment algorithms also raises important questions about the role of PHESGO®. Furthermore, the economic implications of widespread adoption of subcutaneous formulations merit careful evaluation, as PHESGO® has the potential to reduce resource utilization and improve patient satisfaction [26].

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5. Conclusions

Our real-world analysis demonstrates that PHESGO® is effective and well tolerated in HER2 positive breast cancer across disease settings. The pCR rates, safety profile, and metastatic efficacy observed in daily practice are consistent with clinical trial results, supporting PHESGO® as a convenient and valuable option. Exploratory findings regarding sequencing and biomarker interactions suggest avenues for further research, particularly in optimizing therapy for different patient subgroups.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study. Patients are given the opportunity to opt out.

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Abbreviations

The following abbreviations are used in this manuscript:

HER2	human epidermal growth factor receptor 2
pCR	pathological complete response
FISH	fluorescence in situ hybridization
ER	estrogen receptor
PgR	progesterone receptor
IHC	immunohistochemical staining
T-DM1	trastuzumab emtansine
EC	epirubicin and cyclohosphamide
DHP	docetaxel, trastuzumab and perutuzumab
HR	hazard retio

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