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# Real-world clinical outcomes of patients with stage I HER2-positive breast cancer treated with adjuvant paclitaxel and trastuzumab

Veronique Debien [a,*,1], Guilherme Nader Marta [a,1], Elisa Agostinetto [a], Marianna Sirico [b], Flavia Jacobs [c,d], Chiara Molinelli [e,f], Michel Moreau [g], Marianne Paesmans [g], Ugo De Giorgi [b], Armando Santoro [c,d], Donatienne Taylor [h], François P. Duhoux [i], Andrea Botticelli [j], Giacomo Barchiesi [j], Iolanda Speranza [j], Matteo Lambertini [e,f], Hans Wildiers [k,l], Evandro de Azambuja [a], Martine Piccart [a]

[a] Université Libre de Bruxelles (ULB), Hôpital Universitaire de Bruxelles (HUB), Institut Jules Bordet, Brussels, Belgium
[b] IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Meldola, Italy
[c] Department of Biomedical Sciences, Humanitas University, Via Rita Levi Montalcini 4, Pieve Emanuele, 20090 Milan, Italy
[d] IRCCS Humanitas Research Hospital, Humanitas Cancer Center, Via Manzoni 56, Rozzano, 20089 Milan, Italy
[e] Department of Internal Medicine and Medical Specialties (DiMI), School of Medicine, University of Genoa, Genoa, Italy
[f] Department of Medical Oncology, U.O. Clinica di Oncologia Medica, IRCCS Ospedale Policlinico San Martino, Genoa, Italy
[g] Unité de Gestion de l'Information, Institut Jules Bordet, Université Libre de Bruxelles (U.L.B.), Brussels, Belgium
[h] CHU UCL Namur Sainte Elisabeth, Namur, Belgium
[i] Cliniques universitaires Saint-Luc, Brussels, Belgium
[j] Dipartimento di Scienze Radiologiche, Oncologiche e Anatomopatologiche, Università di Roma Sapienza, Rome, Italy
[k] Department of General Medical Oncology, University Hospitals Leuven, Leuven, Belgium
[l] Department of Oncology, KU Leuven - University of Leuven, Leuven, Belgium

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ABSTRACT

Up to 20% of breast cancer overexpress HER2 protein, making it a reliable target for antibody-based treatments. In early HER2-positive breast cancer avoiding anthracycline-based chemotherapy is a challenge. Based on the single-arm phase II APT trial results, adjuvant paclitaxel/trastuzumab is an accepted regimen for patients with stage I HER2-positive disease. In our retrospective study of 240 patients, the median tumor size was 12.0 mm (IQR 9 –15), and 204 (85%) had estrogen receptor-positive disease. After a median follow-up of 4.6 years, 3-year real-world disease-free survival, distant DFS, and overall survival were 98.8% (95% confidence interval (CI), 96.2–99.6), 99.2% (95% CI, 96.7–99.8), and 98.3% (95% CI, 96.2–99.6), respectively. In a real-world setting, an adjuvant paclitaxel/trastuzumab regimen was associated with low recurrence rates among women with stage I, HER2-positive breast cancer. Additionally, we reviewed other treatment optimization strategies attempted or ongoing in HER2-positive breast cancer.

## 1. Introduction

Approximately 15%−20% of early breast cancers (BC) have HER2 overexpression/amplification, a characteristic historically associated with a high risk of recurrence (Witton et al., 2003; Gonzalez-Angulo et al., 2009). The current standard treatment strategy for unselected non-metastatic HER2-positive BC is composed of optimized anti-HER2 targeting in combination with a multi-drug chemotherapy backbone, including anthracyclines or platinum salts. Beyond HER2 status, large tumor size and lymph node involvement are additional prognostic factors. Thus, one treatment option does not fit all HER2-positive populations. The accurate selection of a low-risk population allows to spare them from toxic systemic treatments. Thus, the APT trial, a phase II, single-arm study, addressed the question of treatment optimization in a well-selected population with early HER2-positive disease. The trial enrolled 406 patients with HER2-positive node-negative BC, with tumor

* Corresponding author.
*E-mail address:* veronique.debien@hubruxelles.be (V. Debien).
[1] Equal contributions.

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size up to 3 cm (majority up to 2 cm), to receive adjuvant treatment with weekly paclitaxel for twelve weeks plus trastuzumab for one year (PT regimen). In this trial, this well-tolerated regiment yielded a 3-year invasive disease-free survival (IDFS) rate of 98.7% (95% confidence interval (CI) 97.6–99.8) (Tolaney et al., 2015). The final report showed a 10-year IDFS of 91.3% (95% CI 88.3–94.4), and a 10-year overall survival (OS) of 94.3% (95% CI 91.8–96.8) (Tolaney et al., 2023). Based on those results, PT has been endorsed by several scientific societies and guidelines as a standard adjuvant treatment option for patients with HER2-positive BC with a tumor size between 0.5 and 2 cm without lymph node involvement (Cardoso et al., 2019; Burstein et al., 2021; NCCN, 2022).

Analysis of real-world evidence is an essential part of cancer research. It provides useful insights about the effectiveness of treatments in clinical practice, describes the reliability and transferability of data from trials to community practices, and brings additional data on tolerability in the context of different medical conditions and environmental factors (Di Maio et al., 2020). Our study aimed to report real-world evidence on the efficacy and safety of the PT regimen for the treatment of patients with node-negative HER2-positive BC with a tumor size between 0.5 and 2 cm in Belgian and Italian centers. Our results are presented in light of the summarized discussion about currently available data in a similar setting and overall treatment optimization strategies in early HER2-positive breast cancer.

## 2. Materials and methods

### 2.1. Study design and participants

This retrospective, observational, multicenter study included all consecutive eligible patients treated in 7 selected Belgian and Italian hospitals from January 2014 to December 2018. For this analysis, the cut-off date was chosen to allow a minimal three-year follow-up period for the included patients.

Eligible patients were male and female adults with a confirmed diagnosis of early HER2-positive BC, a tumor size between 5 and 20 mm, and no lymph node involvement (presence of nodal micrometastasis, pNmi, was allowed). HER2 positivity was locally defined as "+ 3" immunohistochemistry (IHC) score or a positive *in situ* hybridization (ISH) according to local assessment. All included patients received at least one dose of adjuvant paclitaxel and trastuzumab combination. Patients treated with regimens containing other cytotoxic (e.g., anthracyclines, platinum) or targeted agents (e.g., pertuzumab) were excluded, as well as those with synchronous contralateral breast tumors, prior (neo)adjuvant systemic therapy for early BC, and prior medical history of BC. The study was approved by local Ethic Committees.

All participating sites extracted data from medical records using the same electronic case report form (RedCap®), including demographics, medical history, tumor and treatment characteristics, and outcomes.

### 2.2. Statistical analysis

Descriptive analyses were used to summarize the characteristics and outcomes of the study population. The study's primary endpoint was a 3-year real-world (rw) DFS (rwDFS), defined as the period between the start of the systemic therapy until the occurrence of locoregional or distant recurrence, any new invasive BC, or death from any cause. Secondary endpoints were distant DFS (rwDDFS), defined from the start of the systemic therapy until distant relapse or death from any cause, and rwOS, defined from the start of the adjuvant treatment until death from any cause.

Assuming the 3-year rwDFS rate to be 95% and that all patients would have a follow-up of at least three years, it was estimated that 250 patients would be required to estimate a 95% confidence interval (95% CI) with a window of + /− 2.5% around the estimated 3-year rwDFS rate. Survival curves were estimated using the Kaplan-Meier method. A $p < 0.05$ was considered statistically significant. SAS software package (version 9.4) was used for data analysis.

## 3. Results

### 3.1. Patients characteristics

A cohort of 240 patients with stage I HER2-positive BC was included in this analysis. The median age at diagnosis was 59.5 years (IQR 50.0–66.9 years), with 170 (70.8%) patients being postmenopausal. Based on the pathology report from surgical samples, the median tumor size was 12.0 mm (IQR 9 – 15 mm), 233 (97.1%) patients had no nodal involvement, 204 (85%) had estrogen receptor (ER)-positive disease (including 2.5% of patients with low ER expression, defined as ER<10% or Allred score 2–3), and 100 (41.7%) had poorly differentiated tumors. Four patients had a negative ISH result, one with IHC 2 + and three with IHC 3 + . Some heterogeneity in HER2 amplification assessment was observed. In Belgium, despite HER2 IHC 3 + , for trastuzumab reimbursement, a confirmation by ISH is required, whereas three patients from Italian sites with IHC 2 + without ISH amplification were treated with trastuzumab. Of note, two of them were diagnosed in 2014 and 2014, when the HER2-equivocal status was an acceptable definition. Table 1 summarizes baseline patients' and tumors' characteristics.

**Table 1**
Baseline characteristics (N = 240).

| | |
|---|---|
| Age at diagnosis – median, years (IQR) | 59.5 (50.0–66.9) |
| BMI (kg/m$^2$) – mean (SD) | 25.1 ( ± 4.4) |
| Comorbidities – N (%) | 76 (31.7) |
| Hypertension | 20 (8.3) |
| Cardiopathies | 10 (4.2) |
| Diabetes | |
| Sex - N (%) | 240 (100) |
| Female | |
| Menopausal status – N (%) | |
| Premenopausal | 68 (28.3) |
| Postmenopausal | 170 (70.8) |
| Unknown | 2 (0.8) |
| Tumor size in mm – median (IQR) | 12.0 (9–15) |
| pT1b | 72 (30.0) |
| pT1c | 168 (70.0) |
| Nodal status – N (%) | 233 (97.1) |
| pN0 | 7 (2.9) |
| pN1mi | |
| Histological type – N (%) | |
| Ductal | 207 (86.3) |
| Lobular | 21 (8.7) |
| Other | 12 (5.0) |
| Grade – N (%) | |
| Grade I | 8 (3.3) |
| Grade II | 132 (55.0) |
| Grade III | 100 (41.7) |
| HER2 IHC – N (%) | |
| IHC 1 + | 5 (2.1) |
| IHC 2 + | 110 (45.8) |
| IHC 3 + | 125 (52.1) |
| HER2 ISH – N (%) | 4 (1.9) |
| ISH not amplified | 163 (67.9) |
| ISH amplified | 73 (30.4) |
| ISH not performed | |
| Estrogen receptor – N (%) | |
| ER positive | 204 (85.0) |
| ER negative | 36 (15) |
| Progesterone receptor – N (%) | 165 (68.7) |
| PR positive | 75 (31.3) |
| PR negative | |

Abbreviations: BMI: body mass index, IHC: immunohistochemistry, IQR: interquartile range, ISH: in situ hybridization, ER: estrogen receptor, PR: progesterone receptor, N: number, SD: standard deviation. *Among 4 cases with ISH not amplified, 2 patients had IHC2 + in 2014 and 2015; equivocal status.

### 3.2. Treatment characteristics

Breast-conserving surgery was the most frequently used surgical procedure for primary tumor treatment (80.8%). The majority of patients underwent sentinel lymph node dissection (96.7%). Adjuvant radiotherapy was performed in 186, accounting for 78.2% of patients. Among premenopausal patients with triple-positive BC, 43.8% received aromatase inhibitors (combined with LHRH analog whenever applicable), whereas only 4.3% of postmenopausal patients received tamoxifen. The mean number of adjuvant weekly paclitaxel and trastuzumab cycles received were 8.4 ( ± 4.1) and 16.4 ( ± 2.5), respectively. The administration of trastuzumab varied, with some sites administering it weekly, as per the APT trial, while the majority administered it every three weeks, even during the chemotherapy period. Only one patient (0.4%) discontinued trastuzumab due to adverse events. Table 2 describes the surgical, systemic, and radiotherapy treatments used in the entire cohort.

### 3.3. Clinical outcome

In our study, the median follow-up was 4.6 years (IQR 3.6–5.6 years). During this follow-up period, there were three disease events (one locoregional and two distant relapses) and four deaths, none of which was related to adverse events or breast cancer recurrence. The 3-year rwDFS was 98.8% (95% CI, 96.2–99.6) (Fig. 1). Two patients with distant bone relapses had hormone-receptor-positive tumors, one grade 3 and one grade 2, without lymph node involvement. Both relapses occurred after more than four years after diagnosis of the primary tumor. The patient with locoregional relapse had Hormone Receptor-positive N0, grade 3 tumor. The 3-year rwOS was 99.2% (95% CI, 96.7–99.8), and the 3-year rwDDFS was 98.8% (95% CI, 96.2–99.6).

## 4. Discussion

In this real-world cohort of patients with HER2-positive BC with tumor size up to 2 cm and no macroscopic nodal involvement, treated with upfront surgery followed by adjuvant paclitaxel and trastuzumab, after a median follow-up of 4.6 years, we observed a 3-year rwDFS rate of 98.8%. Only one local and two distant relapses were observed during the entire follow-up period. We did not identify any patients lost to follow-up at three years after diagnosis. Overall, this adjuvant regimen was well tolerated, with a trastuzumab discontinuation rate due to toxicities of less than 1%.

International guidelines recommend using the combination of weekly paclitaxel and trastuzumab (PT) as a standard adjuvant treatment option for patients with node-negative, HER2-positive small (≤2 cm) tumors (Cardoso et al., 2019). This recommendation is primarily based on the results of the single-arm non-inferiority phase II APT trial (NCT00542451), in which 406 patients with HER2-positive BC with tumors ≤ 3 cm (91.0% had tumor size ≤2 cm), node-negative (1.5% had pN1mic) received weekly treatment with paclitaxel and trastuzumab for 12 weeks, followed by nine months of trastuzumab monotherapy (Tolaney et al., 2015). In this study, the 3-year rate of IDFS was 98.7% (95% CI, 97.6–99.8%) (Tolaney et al., 2015). Recently presented long-term outcomes for this study provide reassurance about the long-lasting efficacy of this regimen. After a median follow-up of 10.8 years, the 10-year IDFS and OS rates were 91.3% and 94.3%, respectively (Tolaney et al., 2022). In the subgroup analysis per HR status, 10-year IDFS remained 91.6% in the HR-positive population (95% CI, 88.0%−95.4%) and 90.6.5% (95% CI, 85.1%−96.4%) for patients with HR-negative disease. The population included in our analysis is similar to the one of the APT study in terms of the main inclusion criteria for the original trial and key prognostic factors, with the exception that patients included in our cohort had lower rates of grade III tumors (56.2% in APT vs. 41.7% in our study) and higher rates of ER positivity (64% vs. 85%). Although cross-study comparisons should always be performed with caution, the IDFS results we observed in our cohort are similar to that demonstrated in the APT trial.

We excluded patients with tumors between 21 and 30 mm and those below 5 mm, corresponding to 9% and 18.9% of the APT trial population, respectively. This decision was supported by the fact that in the most recent guidelines, the cut-off of 20 mm is used for neoadjuvant vs. adjuvant treatment choice. The treatment optimization is not only about treatment de-escalation but also intensification in the high-risk population. The definition of the high-risk population is driven by the tumoral response to neoadjuvant therapy. Indeed, the evaluation of response to neoadjuvant treatment, usually containing anthracycline-based chemotherapy, is essential for the risk assessment. Indeed, it was clearly established that the patients with early HER2-positive BC without pathological complete response defined by Residual Cancer Burden (RCB) 0 have worse outcome (Hamy et al., 2020). Therefore, post-neoadjuvant treatment intensification is justified in patient population with residual disease. The KATHERINE trial (NCT01772472) has demonstrated a 50% risk reduction for invasive disease or death if post-neoadjuvant antibody-drug conjugates (ADC) T-DM1 is administered in this high-risk population (von Minckwitz et al., 2019). Therefore, based on the results of the KATHERINE trial, neoadjuvant chemotherapy might be justified for the risk stratification in post-surgical setting [. Interestingly, up to 13% of patients in the T-DM1 cohort included in this study had a cT1 tumor at presentation, overlapping with the population of the APT study. Thus, the feasibility of optimal upfront surgery should be considered and discussed with patients explaining the excellent outcomes in this highly selected population. In addition to the use of as proposed by the KATHERINE study, the incorporation of tyrosine kinase inhibitors (TKI) has also been studied as treatment intensification strategy and has demonstrated activity in selected patients, particularly those with hormone receptor-positive HER2-positive tumors. In the ExteNET trial, the addition of neratinib in combination with endocrine therapy for one year after the completion of adjuvant trastuzumab increased IDFS (5-year IDFS benefit of 5.1%) among patients with HR-positive tumors. Based on these results, this agent was approved by the US Food And Drug Administration (FDA) and European Medicine Agency (EMA) as adjuvant treatment in this population (Chan et al., 2021). Interestingly, in the ExteNET trial, 31% of the enrolled patients had clinical T1 tumors, and 24% of patients had no lymph node involvement.

The first studies to demonstrate the efficacy of trastuzumab as adjuvant therapy for early HER2-positive BC used combination chemotherapy backbones, usually containing anthracyclines and taxanes (Piccart-Gebhart et al., 2005; Joensuu et al., 2006; Romond et al.,

**Table 2**
Treatment characteristics.

| | |
|---|---|
| Type of breast surgery – N (%) | |
| Breast-conserving | 194 (80.8) |
| Total mastectomy | 46 (19.2) |
| Type of axillary surgery – N (%) | |
| Sentinel lymph node (SLN.) | 232 (96.7) |
| Axillary lymph node dissection (ALND) | 7 (2.9) |
| None | 1 (0.4) |
| Radiotherapy – N (%) | 186 (78.2) |
| Yes | 54 (22.5) |
| No | |
| Type of adjuvant endocrine therapy – N (%) | |
| None | 43 (17.9) |
| Tamoxifen | 34 (14.2) |
| Aromatase inhibitor* | 156 (65.0) |
| Other* * | 7 (2.9) |
| Number of cycles for adjuvant paclitaxel – mean (SD) | 8.4 (4.1) |
| Number of cycles for adjuvant trastuzumab – mean (SD) | 16.4 (2.5) |

* * including premenopausal women receiving LHRH analogs in combination with tamoxifen.

* including premenopausal women receiving LHRH analogs in combination with an aromatase inhibitor.

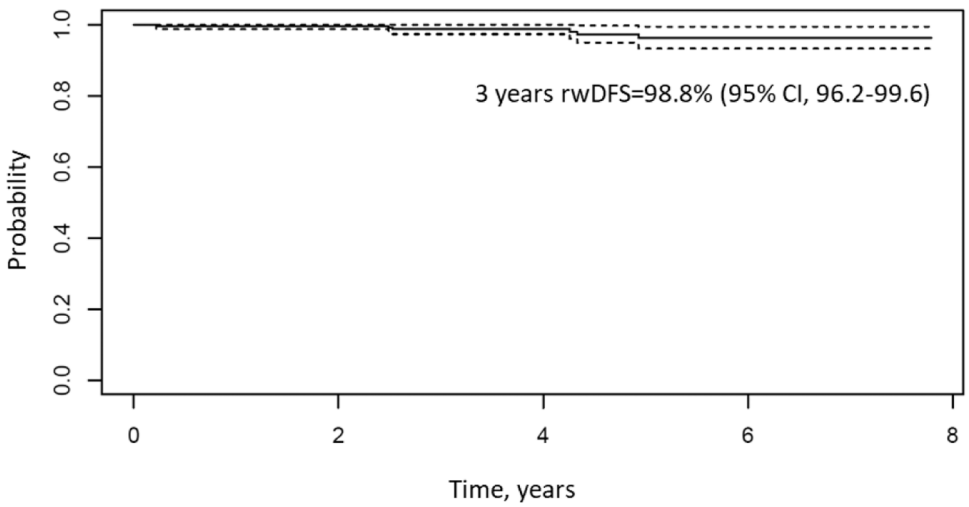


**Fig. 1.** Probability of real-world Disease-Free Survival.

2005). These regimens are associated with a significant risk of early and long-term adverse events, namely cardiac and hematologic, increasing the interest in schemas that were less toxic and equally effective in lower-risk populations. The excellent efficacy and tolerability results observed in the APT trial encouraged the wide incorporation of the PT regimen into clinical practice and its recommendation by several international guidelines. However, limitations related to the study design raised questions about its external validity (Cardoso et al., 2019; NCCN, 2022). The fact that APT was a relatively small, single-arm phase 2 study raised concerns about whether its results would be reproducible and boosted some initiatives aimed at externally "validating" its results. The US FDA performed a patient-level analysis pooling data from 1770 patients with low-risk early HER2-positive BC included in five randomized trials (Amiri-Kordestani et al., 2020). Propensity score matching was used to compare the outcomes of patients treated with PT in the APT trial and those treated with regimens containing trastuzumab with either anthracyclines plus taxanes (ACTH) or carboplatin plus taxanes (TCH). In this study, patients treated with ACTH/TCH regimens had a 3-year IDFS of 96.6%, compared to 98.8% in patients treated with PT (Amiri-Kordestani et al., 2020). In spite of the excellent efficacy results obtained with the PT regimen, some studies have investigated alternative strategies that could potentially retain a similar efficacy with a more favorable toxicity profile. The ATEMPT trial was a phase II study that included patients with stage I, HER2-positive BC, and randomized them to receive either PT or T-DM1 (Tolaney et al., 2021). The co-primary objectives were to compare the incidence of protocol-defined clinically relevant toxicities (CRT) in patients treated with T-DM1 versus PT and to evaluate IDFS in patients receiving T-DM1 (not designed to compare the efficacy between the two arms). At baseline, maximum tumor size was 20 mm, and 75% of hormone-receptor-positive tumors. In this trial, T-DM1 was not associated with less CRT compared with PT, and the 3-year IDFS for T-DM1 and PT were 97.8% and 94.3%, respectively (Tolaney et al., 2021). A recent update shows 5-year iDFS 97.0% for T-DM1 and 91.3% for the trastuzumab arm (Paolo Tarantino et al., 2023). A retrospective study including 173 patients with early HER2-positive BC (mean tumor size of 22 mm) treated with an adjuvant paclitaxel-trastuzumab combination demonstrated a 3-year DFS of 96.6% (Diker et al., 2022). Taken together, these findings confirm the excellent outcomes obtained with adjuvant PT, further supporting the effectiveness of this regimen for the treatment of patients with stage I, HER2-positive BC. Importantly, it has been shown that in a lower-risk population (with small tumors and node negative), more intensified (and more toxic) regimens do not necessarily yield better outcomes. A subanalysis of the adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation (ALTTO) trial assessed the outcomes of 2821 patients with tumors $\leq$ 3 cm and node-negative included in this trial, the majority of whom (93.1%) were treated with anthracycline plus taxane-based combination chemotherapy. In this analysis, the 7-year OS of 95.9% (95% CI, 95.0–96.6%) observed in ALTTO was similar to the one reported in the APT trial (95%; 95% CI, 92.4–97.7) (Tolaney et al., 2019; Nader-Marta et al., 2022).

Exploring risk-adapted neoadjuvant and adjuvant approaches is crucial to improve efficacy while minimizing harmful effects. Omitting anthracyclines chemotherapy during the neoadjuvant setting was explored in the TRAIN-2 trial, in which patients with larger tumors (stage II-III) were enrolled. Carboplatin/paclitaxel trastuzumab was not inferior to standard fluorouracil/epirubicin/cyclophosphamide, followed by paclitaxel/trastuzumab in terms of pathological complete response (pCR) nor even event-free survival (van der Voort et al., 2021). A biomarker-guided de-escalation strategy was studied in the PHERGain study, a randomized, phase II trial, exploring the possibility to de-escalate systemic treatments in neoadjuvant based on the metabolic response assessed by 18 F-fluorodeoxyglucose (18 F-FDG)-PET (Pérez-García et al., 2021). In this study, patients were randomly assigned to receive either docetaxel/carboplatin /trastuzumab /pertuzumab (group A) or only dual anti-HER2 blockade with trastuzumab/pertuzumab (group B). Patients with stage I BC comprised 13% and 8% of those included in groups A and B, respectively. After two cycles, 18 F-FDG-PET was performed to assess treatment response, which was defined as a decrease by at least 40% of the baseline standardized uptake value (SUV). In this study, 37.9% of patients classified as responders had a pCR with a chemotherapy-free regimen, demonstrating that metabolic response might also be used to inform de-escalation strategies. The PHERGAIN-2 (NCT04733118) is an ongoing phase II study evaluating three cohorts chemotherapy-free regimens. In the ADAPT trial, patients with HER2-positive hormone receptor-positive early BC (approximately half of which with stage I disease) were randomly assigned to receive either trastuzumab plus endocrine therapy, or T-DM1 with or without endocrine therapy (Harbeck et al., 2017). pCR rate was higher with T-DM1, regardless of the combination with endocrine therapy. About half of the enrolled patients had clinical stage I disease.

Several ongoing studies are also exploring different strategies that might help us better understand the optimal treatment approaches in each scenario. DECRESCENDO (NCT04675827) is an ongoing dual-phase single-arm phase II de-intensification study in which patients receive neoadjuvant taxane in combination with trastuzumab and pertuzumab fixed-dose combination (FDC) administrated subcutaneously. The adjuvant therapy is based on pathological response: patients who achieve a pCR, defined as Residual Cancer Burden (RCB)= 0, receive adjuvant pertuzumab and trastuzumab FDC for 14 cycles, while those

with residual disease receive T-DM1 for 14 cycles (with the possibility of adding anthracycline-based chemotherapy in case of RCB $\geq$ 2) (Debien et al., 2022). The CompassHER2 trials (NCT04457596, NCT04266249) are also assessing adjuvant strategies determined by the pathologic response to neoadjuvant therapy. In CompassHER2-RD, patients with residual disease are randomized to receive either the combination of T-DM1 plus tucatinib or T-DM1 as monotherapy. In CompassHER2-pCR, patients with no residual disease will receive adjuvant trastuzumab and pertuzumab. ATEMPT 2.0 is randomizing patients to receive either PT regiment or T-DM1 for 6 cycles (18 weeks) followed by trastuzumab for additional 11 cycles (NCT04893109). The phase II ADEPT trial is a single-arm study enrolling patients with stage I triple-positive breast cancer to receive adjuvant endocrine therapy, pertuzumab, and trastuzumab (NCT04569747).

A Chinese study, IRIS (NCT04383275), aims to assess the efficacy of capecitabine as an adjuvant partner of trastuzumab for stage I early HER2-positive BC. In addition to the response to neoadjuvant therapy, other biomarkers under development may, in the near future, inform risk-adapted management strategies based on tumor biology. The levels of tumor-infiltrating lymphocytes (TILs) have been shown to predict pCR and event-free survival in patients treated with a neoadjuvant anti-HER2 blockade in combination with chemotherapy in the NeoALTTO trial (Salgado et al., 2015). The APT trial cohort was used to investigate the immune landscape of small HER2-positive tumors (Barroso-Sousa et al., 2019). In this analysis, various aspects of the tumor microenvironment, including TIL, PD-L1 expression, and immune signatures were evaluated. Consistent with previous findings in HER2-positive disease, hormone receptor-negative tumors exhibited higher TIL infiltration than hormone receptor-positive tumors. Interestingly, high TIL levels were also associated with specific immune cell signatures, such as B cell and Th1. In the ADAPT trial, which focused on HER2-positive hormone-receptor-positive tumors treated with T-DM1, patients with HER-enriched intrinsic subtype achieved a higher pCR rate (54% in HER2-enriched versus 28% for luminal or basal-like subtypes) (Harbeck et al., 2021). More recently, HER2DX, an assay that integrates clinical data (tumor size and nodal status) with biological information related to immune response, luminal differentiation, tumor cell proliferation, and expression of the HER2 17q12–21 chromosomal amplicon has also shown prognostic value in early HER2-positive BC (Tolaney et al., 2022; Prat et al., 2022; Guarneri et al., 2022). Finally, the treatment landscape for early HER2-positive BC might be influenced by ongoing studies (e.g., DESTINY-Breast11-NCT05113251) testing novel ADC that have shown unprecedented activity in patients with HER2-low disease in the metastatic setting, challenging the traditional HER2-positivity definition as a mandatory requirement for the use of HER2-targeted agents (Modi et al., 2022).

Our study has some limitations. Firstly, intrinsic biases associated with its retrospective design, with a relatively limited follow-up period, the strict inclusion criteria used to match the population in the APT trial, and the number of patients included should be considered while interpreting our results. Secondly, we observed different clinical practices among participating sites: related to the HER2 amplification assessment and treatment administration. The combination of Luteinizing Hormone-Releasing Hormone (LHRH) analogs and aromatase inhibitors might also have an impact on the disease event in the HR-positive premenopausal population. In addition, some patients refused or omitted the standard treatments, e.g., radiotherapy after partial mastectomy in six patients. Finally, because of the low number of events, we could not perform any subgroup analysis. Regarding safety, we did not collect data about chemotherapy-related toxicities.

Despite these aspects, to our knowledge, this is the largest multicentric cohort validating the efficacy and safety of the PT regimen in a real-world setting, including a homogeneous population of patients with stage I HER2-positive BC.

In conclusion, our study demonstrates that adjuvant paclitaxel plus trastuzumab treatment is associated with low recurrence rates among women with stage I HER2-positive BC in a real-world setting.

However, a longer follow-up is desirable to confirm these results particularly in the ER-positive tumor population.

## Declaration of Competing Interest

VD, MS, FJ, MM, MP, IS, WH: none.

GNM: Travel grants for meetings from Roche and Bayer, outside the submitted work.

EA: Speaking fee/consultancy: Eli Lilly, Sandoz, AstraZeneca. Support to attend medical conferences from Eli Lilly, Roche, Novartis, Genetics, Istituto Gentili, Daiichi Sankyo (all outside the present work).

CM: receive fees from Novartis and Lilly outside the submitted work. Ugo De Giorgi received honoraria for advisory boards or speaker fees for Pfizer, BMS, MSD, PharmaMar, Astellas, Bayer, Ipsen, Roche, Novartis, Clovis, GSK, AstraZeneca, Institutional research grants from AstraZeneca, Sanofi and Roche all outside the submitted work.

UDG: Advisory boards: Astellas, Bayer, BMS, Ipsen, MSD, Novartis, Pfizer, PharmaMar, Roche; Institutional research grant: AstraZeneca, Roche, Sanofi.

AS: Advisory Board: BMS (BRISTOL-MYERS-SQUIBB), Servier, Gilead, Pfizer, Eisai, Bayer, MSD (MERCK SHARP & DOHME); Consultancy: Arqule, Sanofi, Incyte; Speaker's Bureau: Takeda, BMS, Roche, Abbvie, Amgen, Celgene, Servier, Gilead, Astrazeneca, Pfizer, Arqule, Lilly, Sandoz, Eisai, Novartis, Bayer, MSD.

DT: advisory board: Agendia, AstraZeneca, Daiichi Sankyo, Eli Lilly, Medscape, MSD, Novartis, Roche; Travel: AstraZeneca,Pfizer, Roche.

FPD: Advisory Board: Amgen, AstraZeneca, Daiichi Sankyo, Gilead Sceince, Lilly, Novartis, Pfizer, Pierre Fabre, Roche, Seagen; Contracted Research: Fondation belge contre le cancer; Institutional grant: AstraZeneca.

AB: Advisory board: Argen, BMS, Eli-Lilly, MSD, Novartis, Pfizer, Roche.

GB: Advisory board: BMS, Eli Lilly, MSD, Novartis, Pfizer, Roche; Travel: BMS, Eli Lilly, MSD, Novartis, Pfizer, Roche.

ML: reports advisory role for Roche, Lilly, Novartis, Astrazeneca, Pfizer, Seagen, Gilead, MSD and Exact Sciences; speaker honoraria from Roche, Lilly, Novartis, Pfizer, Sandoz, Libbs, Daiichi Sankyo and Takeda; Travel Grants from Gilead; Research funding (to the Institution) from Gilead outside the submitted work.

EdA: Honoraria and/or advisory board from Roche/GNE, Novartis, SeaGen, Zodiac, Libbs, Pierre Fabre, Lilly, Astra-Zeneca; travel grants from Roche/GNE and Astra-Zeneca; Research grant to my institution from Roche/GNE, AstraZeneca, and GSK/Novartis.

MP: Board Member (Scientific Board): Oncolytics; Consultant (honoraria): AstraZeneca, Camel-IDS/Precirix, Gilead, Immunomedics, Lilly, Menarini, MSD, Novartis, Pfizer, Roche-Genentech, Seattle Genetics, Immutep, Seagen, NBE Therapeutics, Frame Therapeutics; Research grants to my Institute: AstraZeneca, Immunomedics, Lilly, Menarini, MSD, Novartis, Pfizer, Radius, Roche-Genentech, Servier, Synthon.

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**Veronique Debien, MD, MSc**: She has a medical degree obtained from the University of Strasbourg, France, and a Master of Science degree in research in Biomedicine. She performed her medical oncology specialization at the University Hospital of Strasbourg, Institut de Cancéerologie Strasbourg, and Institut Gustave Roussy (Villejuif, France). She is currently a postdoctoral research fellow at Institut Jules Bordet (Brussels, Belgium.) Clinical research with an emphasis on academic-promoted studies is the core of her research work. She is actively involved in conducting phase II clinical trials in breast and bladder cancer and leading research projects. Her clinical activity is focused on breast cancer and early drug development. She is an author and co-author of around ten peer-reviewed publications and has presented her work at different poster sessions at the San Antonio Breast Cancer Symposium, ASCO, and ESMO annual congresses. She is a Ph.D. candidate in Biomedicine at Université Libre de Bruxelles. She is an ESMO, ASCO, and AACR member and a young investigator in Breast and Genito-Urinary Groups at EORTC.

**Guilherme Nader Marta:** he received his medical degree from the University of Sao Paulo (Brazil) and completed his oncology residency in the same institution. Since 2021, he has joined Jules Bordet Institute in Belgium as a clinical research fellow, where his time is dedicated to breast cancer research. He is currently a Ph.D. candidate at the Universite Libre de Bruxelles (ULB) with a research line in biomarkers and breast cancer, special histological types, particularly lobular breast cancer. The results of his research have been presented at international conferences, published in peer-reviewed journals, and recognition for the high quality of his work. He received a Conquer Cancer Merit Award in 2022 and a Young Investigator Award in 2023.

**Elisa Agostinetto, MD:** she is a medical oncologist and researcher in the field of breast cancer. She received her medical degree in Italy at the University of Udine. She completed her training in medical oncology in Milan, Italy, and afterwards, she moved to Brussels, Belgium, where she is currently pursuing an advanced research fellowship at Institut Jules Bordet - Université Libre de Bruxelles. She is the author of more than 50 articles published in peer-reviewed journals. Her research works have been presented at several international

oncology conferences, including ASCO, ESMO and SABCS. She is an ESMO, ASCO member, and a young investigator in the EORTC Breast Cancer Working Group.

**Marianna Sirico, MD:** is a Medical Oncologist Specialist currently working at the IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori" (Meldola, Italy). She is involved in patient care and clinical research, with a main focus on hormone receptor-positive disease and the discovery and development of early prognostic and predictive biomarkers.

**Flavia Jacobs, MD:** is a young oncologist in her fifth year of residency program. She completed her degree in medicine and surgery at the University of Study in Palermo in 2017 and later moved to Milan to pursue further studies in oncology. Throughout her career, Dr. Jacobs has demonstrated a keen interest in breast cancer, actively engaging in various academic projects focused on breast cancer research and management. To enhance her expertise, Dr. Jacobs dedicated her final year of residency to a medical fellowship at the prestigious Institute Jules Bordet in Brussels. This experience provided her with knowledge and experience in clinical trials, significantly expanding her understanding of breast cancer treatment strategies.

**Chiara Molinelli, MD:** is a Medical Oncology Fellow, currently working at Ospedale Policlinico San Martino in Genova under the supervision of her mentors Professor Lucia Del Mastro and Professor Matteo Lambertini. She is focused on the care of breast cancer patients and is deeply involved in breast cancer research in early and metastatic settings. During her European fellowship at Jules Bordet Institute with Professor Evandro de Azambuja, she conducted a systematic review and meta-analysis on the prognostic and predictive value of HER2-Low status in breast cancer. She also presented some abstracts at national and international meetings.

**Michel Moreau, MD, MSc:** has a medical degree obtained from the UCL (Université Catholique de Louvain), a master in Tropical Medicine obtained from the Tropical Institute in Antwerp, and a master of Science in Public Health, Epidemiology, and Statistics obtained from the Free University of Brussels. He is working as an epidemiologist in the information management unit and contributes as a statistician to clinical research projects at Institut Jules Bordet (belonging to Hôpital Universitaire de Bruxelles, Brussels, Belgium). He has co-authored more than 100 peer-reviewed papers.

**Marianne Paesmans, MSc:** She has a master in mathematics, a third-degree master in actuarial sciences, and a third-degree master in management of care institutions, all delivered by the Free University of Brussels. She is head of the information management unit, and she contributes as a statistician to clinical research projects, including but not limited to clinical trials at Institut Jules Bordet (belonging to Hôpital Universitaire de Bruxelles, Brussels, Belgium. She has co-authored over 400 abstracts (> 100 oral presentations) and more than 350 peer-reviewed papers.

**Ugo De Giorgi, MD, Ph.D.:** is a Medical Oncologist Specialist at the Department of Medical Oncology of the IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori" (Meldola, Italy). He is the current head of the Uro-Gynecologic, Breast, and Oncologic High Dose Innovative Treatments Units. Winner of numerous research awards and scholarships, which allowed him to experience in the Netherlands and the United States, he is the author of over 350 international publications, has the qualification of a Full Professor of Oncology in Italy, and is a lecturer at several Specialization Schools of the University of Ferrara. He holds positions of responsibility in oncological scientific societies, including AIOM, IGG, and Meet-uro, where he was recently appointed President.

**Armando Santoro, MD, Ph.D.:** is Chief in the Department of Oncology and Hematology Unit at Humanitas Research Hospital in Milan. After the medical degree at the University of Messina in 1974, he furthered his expertise by obtaining the Certificat de Cancerologie Clinique et Experimentale from the University of Paris in 1976, specializing in Hematology at the University of Rome in 1977, and Oncology at the University of Genoa in 1980. In terms of academia, Prof. Santoro has been an Adjunct Professor at the School of Specialization in Oncology of the University of Milan since 2004. His knowledge and extensive experience in oncology and hematology have established him as a distinguished leader, greatly impacting the medical community.

**Donatienne Taylor, MD:** is a medical oncologist (MD at UCLouvain, Belgium). After completing her specialization, she built her career at the University hospital of UCL Namur, focusing on breast and gastrointestinal cancers. She is principal investigator or several ongoing clinical trials in breast cancer.

**François P Duhoux, MD, Ph.D:** a medical oncologist (MD and Ph.D. at UCLouvain, Belgium). His main domains of competence are breast cancer and oncogenetics. He is an active member of the Belgian Society of Human Genetics (BeSHG), BSMO, ASCO, ESMO, AACR and the Belgian Society of Senology. He also received ASCO Foundation Merit Awards (in 2009 and 2011), and a Pfizer Educational Grant in 2011.

**Andrea Botticelli, MD, Ph.D.:** is an assistant professor, medical oncologist, and researcher in the field of breast cancer and head and neck cancer. He received his medical degree at Sapienza University. He completed his training in Medical Oncology and Ph.D. in Ospedale Sant'Andrea, Rome. Afterward, he moved to Policlinico Umberto I, Rome. He is the author of more than 120 articles published in peer-reviewed journals. His research works have been presented at several international oncology conferences, including ESMO, ASCO, and SABCS. He coordinates the Breast Unit of Policlinico Umberto I. He is an ASCO member.

**Giacomo Barchiesi, MD:** is a medical oncologist and researcher in the field of breast cancer and gynecological cancers. He received his medical degree at Sapienza University in Rome. He completed his training in Medical Oncology in Prato, Italy; afterward, he worked as a medical oncologist in IFO, Rome, and Mestre Hospital. He is the author of 21 indexed publications. He is an ASCO member.

**Iolanda Speranza, MD:** is a medical oncologist dedicated to breast and urogenital cancer patients. She spent her entire career as a medical oncologist in Policlinico Umberto I, Rome.

**Matteo Lambertini, MD, Ph.D:** is Associate Professor and consultant in medical oncology at the University of Genova – IRCCS Ospedale Policlinico San Martino in Genova (Italy). He is mainly focused on the care of breast cancer patients and is deeply involved in breast cancer research. Above all, he has particular expertise in the management of breast cancer in young women, with specific attention to the fertility and pregnancy-related issues that they have to face after diagnosis. In 2018 he completed his Ph.D. at the Universite Libre de Bruxelles (U.L.B.) in Brussels (Belgium). He has been an active ESMO member since October 2011. He was awarded the following ESMO Fellowships: Translational Research Unit Visit in 2012, Clinical Unit Visit in 2013, and Translational Research Fellowship in 2016–2018. In 2017, he attended the ESMO Leaders Generation Program. He has served on the ESMO Press & Media Affairs Committee and the ESMO Breast Cancer Faculty. He is currently a member of the ESMO Young Oncologists Committee and is an Associate Editor for ESMO Open Cancer Horizons. He has authored more than 220 publications in peer-reviewed journals and book chapters.

**Hans Wildiers, MD, Ph.D.:** is a medical oncologist dedicated to breast cancer research and geriatric oncology. He has been a staff member at the Department of medical oncology at the University Hospital Leuven, Belgium, since 2004. He coordinates the Leuven multidisciplinary breast center since 2015. He has been the coordinator of several academic studies in the field of breast cancer and geriatric oncology and is the author of more than 200 peer-reviewed papers. He has been active on the board of SIOG, the International Society of Geriatric Oncology, for many years and serves this organization as president from November 2018 till October 2020. From 2009–2015, he chaired the elderly task force Cancer of the Elderly of the European Organisation for Research and Treatment of Cancer (EORTC). In 2023, Prof Wildiers received the B.J. Kennedy Geriatric Oncology Award at the 2023 ASCO Annual Meeting.

**Evandro de Azambuja, MD, Ph.D: is a Medical Oncologist focusing on breast cancer. He is** the Head of the Medical Support Team (Academic Promoting Team) located at the Jules Bordet Institute in Brussels, Belgium. Dr. de Azambuja earned his first PhD from the Federal University of Rio Grande do Sul, Porto Alegre, Brazil, in May 2007 and his second PhD from the Université Libre de Bruxelles (U.L.B) in December 2015. He is deeply involved in the conduct of large phase III trials in breast cancer (some of them practice changing), such as HERA (adjuvant trastuzumab), ALTTO (trastuzumab and/or lapatinib), APHINITY (trastuzumab with or without pertuzumab), Alexandra (adjuvant atezolizumab in triple-negative breast cancer), Olympia (adjuvant Olaparib). He is also engaged in studies concerning cancer toxicity of new drugs in oncology as well as in long-term follow-up of patients enrolled in clinical trials, with a focus on cardiotoxicity. Dr. de Azambuja is highly involved in the ESMO in his position as ESMO Director of Membership, ESMO Executive Board, ESMO Council, and the ESMO Leaders Generation Programme faculty member. He is the current president of the Belgian Society of Medical Oncology (BSMO). He has (co)-authored around 255 peer-reviewed articles and 15 book chapters. He has been a member of the Education and Scientific Committees of the ESMO Congress, ESMO Breast, EBCC, and ECCO meetings and has been an invited international speaker at a number of conferences and countries.

**Martine Piccart, MD, Ph.D:** is Professor of Oncology at the Université Libre de Bruxelles (ULB) and Scientific Director at the Jules Bordet Institute in Brussels, Belgium. Earning her medical degrees at the ULB and oncology qualifications in New York and London, she is also member of the Belgian Royal Academy of Medicine. With a primary interest in breast cancer and drug development, Prof. Piccart is a leader in international research collaboration and is the principal or co-principal investigator of many clinical trials, including HERA, MINDACT and ALTTO. She is co-founder and Chair of the Breast International Group (BIG), uniting 49 academic research groups from around the world and running over 30 trials under its umbrella. Prof. Piccart was President of ESMO (2012–2013) and ECCO (2014–2015). She is a member of the ESMO Magnitude of Clinical Benefit Scale Working Group and active in numerous professional organisations. She is a former president of EORTC and served on the ASCO Board. She is (co) author of more than 390 publications in peer-reviewed journals, she has received numerous prestigious awards for her research contributions, including the Jill Rose Award (New York), the William L. McGuire Award (San Antonio) and, recently, the Umberto Veronesi Award for the Future Fight against Cancer (Cancun).