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ORIGINAL ARTICLE

Palbociclib plus letrozole versus weekly paclitaxel, both in combination with trastuzumab plus pertuzumab, as neoadjuvant treatment for patients with HR-positive/HER2-positive early breast cancer: primary results from the randomized phase II TOUCH trial (IBCSG 55-17)☆

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Background: Hormone receptor (HR)-positive/human epidermal growth factor receptor 2 (HER2)-positive breast cancer (BC) is a heterogeneous disease with low pathological complete response (pCR) to standard neoadjuvant treatment. Cyclin-dependent kinase 4 and 6 inhibitors with endocrine and anti-HER2 therapy have shown a potential for chemotherapy omission in this context.

Patients and methods: TOUCH is an international, open-label, phase II trial for postmenopausal patients with cT >1 cm, cN0 or cN1, HR-positive/HER2-positive BC, randomly assigned to 16 weeks of neoadjuvant weekly paclitaxel or palbociclib and letrozole, both with trastuzumab + pertuzumab (HP). The primary objective investigated the interaction between a gene signature of E2F pathway activity (RBsig) and pCR (ypT0N0 or ypTisN0), hypothesizing higher pCR for RBsig-high tumors in the paclitaxel + HP group and for RBsig-low tumors in the palbociclib + letrozole + HP group. RBsig was assessed by RNA-sequencing from pre-treatment biopsies; intrinsic subtypes were estimated by absolute intrinsic molecular subtyping Treatment-by-biomarker interaction was estimated using logistic regression in 115 assessable patients.

Results: A total of 147 patients were randomly assigned (74 paclitaxel + HP, 73 palbociclib + letrozole + HP) and 145 constituted the treated population, with a median age of 69 years (interquartile range 63-73 years). More patients completed palbociclib versus paclitaxel (94.4% versus 79.5%). The most frequent grade 3-4 adverse events were neutropenia and diarrhea (6.9% versus 43.1% and 11% versus 8.3% in the paclitaxel + HP versus the palbociclib + letrozole + HP groups, respectively). The pCR rate was 32.9% [95% confidence interval (CI) 22.3% to 44.9%] in the paclitaxel + HP group and 33.3% (95% CI 22.7% to 45.4%) in the palbociclib + letrozole + HP group. No significant

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☆Note: This study was previously presented at San Antonio Breast Cancer Symposium, San Antonio, TX, USA, 11 December 2024.

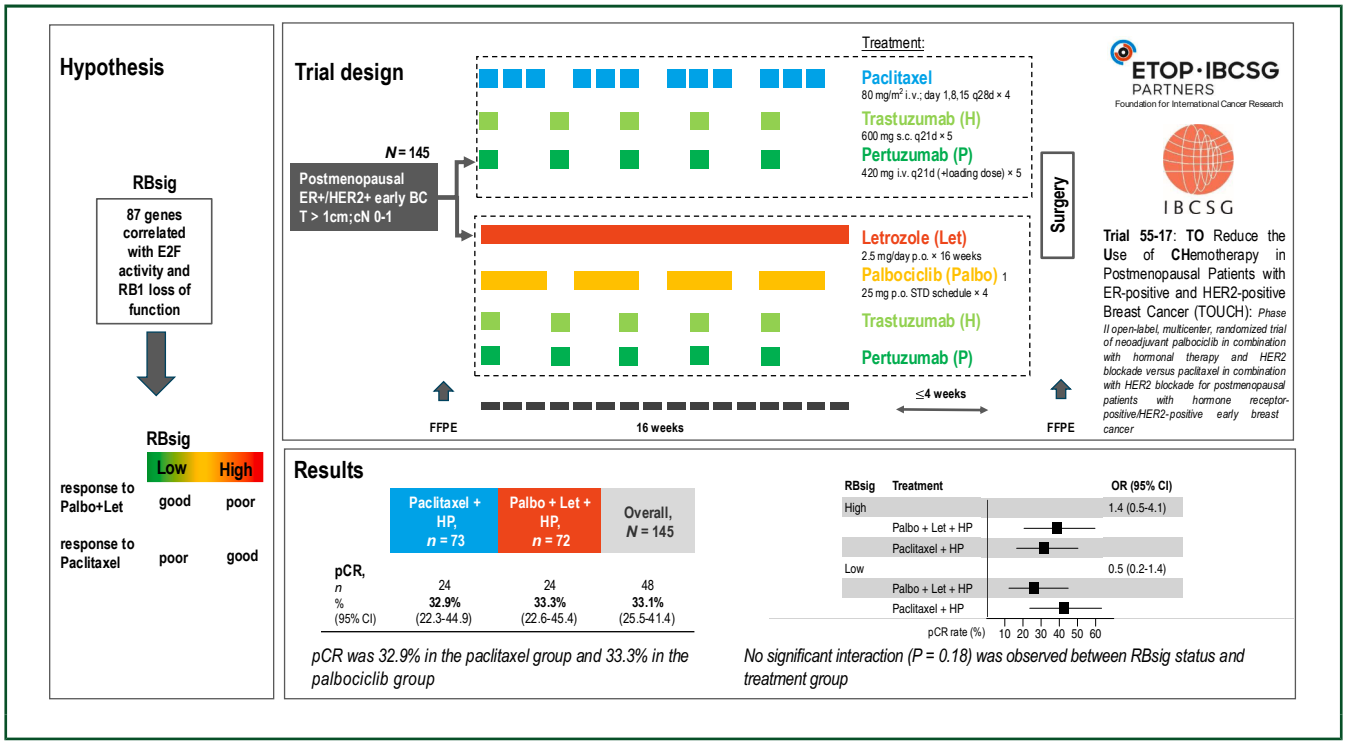
TOUCH collaborators are provided in the Supplementary Appendix.

treatment-by-RBsig interaction was observed ($P = 0.18$): pCR in RBsig high versus low was 31.3% (95% CI 16.1% to 50.0%) versus 42.3% (95% CI 23.4% to 63.1%) in the paclitaxel + HP group, and 38.5% (95% CI 20.2% to 59.4%) versus 25.8% (95% CI 11.9% to 44.6%) in the palbociclib group. pCR was higher in non-luminal versus luminal subtypes (45.5% versus 18.4%), with no interaction with treatment.

Conclusions: Although the primary hypothesis was not supported, TOUCH shows that dual anti-HER2 blockade with a chemotherapy-free backbone of palbociclib + letrozole yields pCR rates similar to paclitaxel, representing an attractive alternative treatment strategy.

Key words: early breast cancer, hormone receptor positive, HER2 positive, neoadjuvant therapy, chemotherapy de-escalation, CDK4/6 inhibitor

GRAPHICAL ABSTRACT



INTRODUCTION

Human epidermal growth factor receptor 2 (HER2)-overexpressed and/or -amplified breast cancer (BC) encompasses 15%-20% of all breast tumors. More than 50% of HER2-positive BCs co-express estrogen receptors (ERs).[1] In patients diagnosed with stage II-III HER2-positive BC, chemotherapy (CT) combined with anti-HER2 monoclonal antibodies [trastuzumab + pertuzumab (HP)] is the standard of care.[2] Advances in HER2-targeted therapies offer a good opportunity to de-escalate CT regimens, especially in the neoadjuvant setting, considering that pathological complete response (pCR) is a patient-level surrogate for long-term outcomes.[3] Dual HER2 blockade with HP combined with docetaxel results in a higher pCR rate compared with trastuzumab alone in combination with the same CT backbone. However, the efficacy of this regimen seems to be less important in patients with ER-positive/HER2-positive cancers (pCR of 26% compared with 63.2% in ER-negative cancers).[4] Few trials investigated the addition of endocrine therapies (ETs) with HER2-targeted treatments in patients with ER-positive/HER2-positive BC. The combination of trastuzumab + lapatinib (dual HER2 and epidermal growth factor receptor tyrosine kinase inhibitor) + ET (letrozole) yielded a pCR rate of only 21% in a small cohort of 39 patients with ER-positive/HER2-positive BCs.[5]

Cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors (abemaciclib, palbociclib and ribociclib) improve progression-free survival (PFS) in ER-positive/HER2-negative advanced BC when combined with ET compared with ET alone.[6] Abemaciclib and palbociclib in combination with trastuzumab and ET have shown clinical activity in women with metastatic ER-positive/HER2-positive BC whose disease had previously progressed on other anti-HER2-based regimens.[7,8] Recently, results from the PATINA trial showed that, in patients with ER-positive/HER2-positive metastatic BC responding to an induction CT with

a taxane + HP, adding palbociclib to a maintenance treatment consisting of ET in combination with HP greatly improves PFS.[9]

The main mechanism of action of CDK4/6 inhibitors is the suppression of retinoblastoma (RB) phosphorylation, enforcing G_1 cell cycle arrest. Functional RB is required for the efficacy of CDK4/6 inhibitors.[10] One of the most widely described mechanisms of primary and acquired resistance to CDK4/6 inhibitors is the genomic loss of *RB1* alleles and/or loss-of-function *RB1* mutations.[11-14]

We previously described a gene signature of E2F-dependent genes, which is correlated with functional loss of *RB1* (RBsig) and able to predict response to the CDK4/6 inhibitor palbociclib in BC cell lines. Those with elevated levels of RBsig (RBsig high) were among the most resistant to palbociclib treatment.[15] Moreover, RBsig appeared to be also predictive of response to CT + trastuzumab in patients with ER-positive/HER2-positive BC. Indeed, the pCR rate after neoadjuvant CT + anti-HER2-targeted treatment was significantly lower in tumors with RBsig-low expression compared with those with RBsig-high expression. These data suggest that RBsig identifies a subset of HR-positive/HER2-positive BCs (RBsig low) deriving little benefit from CT.[16] Taken together, these data suggest that among ER-positive/HER2-positive BCs, those with RBsig-high tumors might derive benefit from CT and be resistant to CDK4/6 inhibitors. Conversely, those with RBsig-low tumors who derive little benefit from CT might benefit from CDK4/6 inhibitors.

To validate this hypothesis, we conducted a randomized phase II trial in postmenopausal women diagnosed with ER-positive/HER2-positive BC who were candidates for neoadjuvant systemic treatment, who were randomly assigned to receive paclitaxel or palbociclib plus letrozole, both in combination with dual HER2 blockade with HP.

PATIENTS AND METHODS

Study design and conduct

TOUCH (EudraCT: 2017-005067-40; ClinicalTrials.gov: NCT03644186) is an international, multicenter, phase II trial that randomly assigned postmenopausal women with ER-positive, HER2-positive primary BC to receive paclitaxel or the combination of the CDK4/6 inhibitor palbociclib plus letrozole, both regimens in combination with HP, during a treatment period of 16 weeks before surgery. Eligible patients had previously untreated, histologically confirmed early BC with tumors >1 cm (cT1c-T3), with no clinical nodal involvement (cN0) or nodal involvement limited to clinically or radiologically detectable metastases to movable ipsilateral level I, II axillary lymph node(s) (cN1), classified according to local histopathology as ER positive (ER ≥ 10%) and HER2 positive by immunohistochemistry or FISH. The trial commenced enrollment on 16 April 2019, with eligibility limited to older patients (aged ≥65 years). A protocol amendment (18 February 2020) expanded eligibility to include postmenopausal patients regardless of their age. Complete eligibility and exclusion criteria are provided in Supplementary Methods, available at https://doi.org/10.1016/j.annonc.2025.10.016, and in the TOUCH Protocol Amendment 2.[17]

According to random assignment, open-label treatment consisted of paclitaxel 80 mg/m^2 intravenously (i.v.) on days 1, 8 and 15 every 28 days for four cycles, or palbociclib 125 mg/day orally for 21 days followed by 7 days' rest for four 28-day cycles plus letrozole 2.5 mg/day orally for 16 weeks. All patients received trastuzumab 600 mg subcutaneously every 3 weeks and pertuzumab 840 mg i.v. loading dose followed by 420 mg i.v. every 3 weeks, both for a total of five doses. Patients then proceeded to surgery according to standard of care.

Before the amendment, 35 patients aged ≥65 years were enrolled. For randomization, these patients were stratified by G8 score[18,19] (>14 versus ≤14) and nodal status (cN0 versus cN1). After the amendment, 112 postmenopausal patients of any age were eligible for enrollment, although G8 was only required for those aged ≥65 years, and the stratification factors were age plus G8 score (<65 years versus ≥65 years and G8 score >14 versus ≥65 years and G8 score ≤14) and nodal status (cN0 versus cN1). Patients were randomly assigned in a ratio of 1 : 1; dynamic institution balancing was used to balance randomized assignments within 37 institutions.

All patients provided written informed consent. Local ethics committees and appropriate health authorities approved the protocol. The trial was conducted according to the ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines.

In total, 147 patients were enrolled and randomly assigned. Two patients withdrew consent before starting any protocol treatment. The remaining 145 patients who received at least one dose of trial medication constituted the treated population. The assessable population consisted of 115 patients whose RBsig status was successfully determined from a pre-treatment biopsy sample and who received at least one full dose of trial medication [Figure 1, Consolidated Standards of Reporting Trials (CONSORT) diagram].

Baseline clinical T stage was not captured in case report forms directly and was determined from the maximum tumor diameter measured by mammography or ultrasound. When both mammography and ultrasound were documented, the largest measurement was used.

pCR (ypT0N0 or ypTisN0) was determined from the local histopathological evaluation according to the American Joint Committee on Cancer (AJCC) Staging Manual and was defined by the absence of invasive carcinoma in the breast and lymph nodes. The presence of *in situ* carcinoma after trial treatment in the absence of residual invasive disease constituted a pCR. (AJCC eighth edition was current during the trial.) The presence of tumor within lymphatic and/or vascular spaces in the breast (lymphatic vascular invasion) with or without other residual invasive cancer precluded classification as a pCR. Patients who did not undergo surgery were considered as not having pCR. pCR in breast only (bpCR) was defined as ypT0/ypTis. Tumor evaluation by

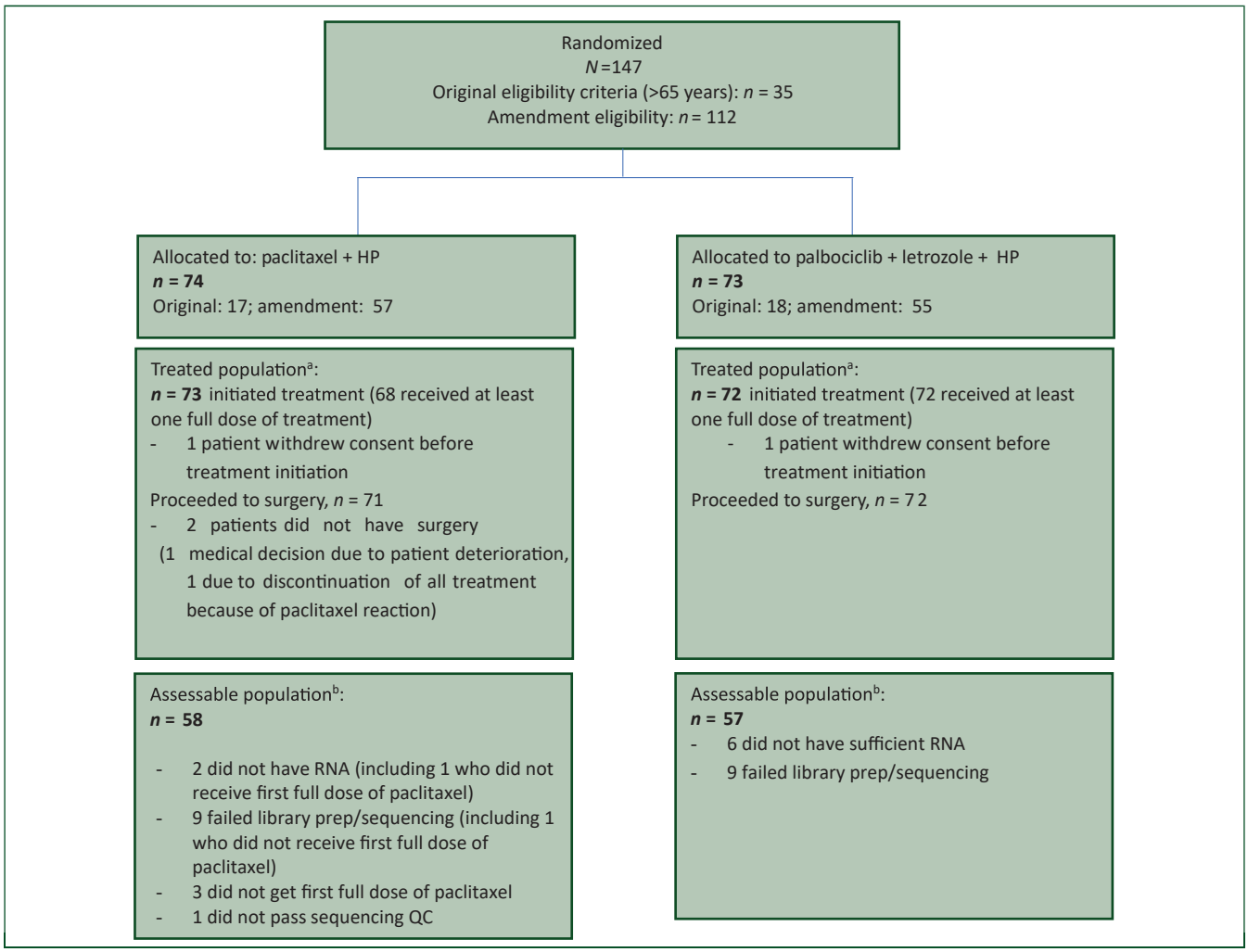


Figure 1. CONSORT flow diagram. $n = 5$ patients discontinued paclitaxel at first cycle due to infusion reactions ($n = 4$) and grade 3 muscle cramp ($n = 1$) and therefore did not receive a first full paclitaxel dose; these five patients are included in the treated population but are excluded from the assessable population. CONSORT, Consolidated Standards of Reporting Trials; HP, trastuzumab + pertuzumab; QC, quality control.
[a]The treated population includes randomized patients who received at least one dose of trial medication (i.e. those who initiated any study treatment).
[b]The assessable population includes randomized patients who had evaluable RBsig and received at least one full dose of trial medication.

physical examination and imaging (bilateral mammography and breast ultrasound) was mandatory at study entry and before surgery; after two cycles of treatment, only physical examination was required. Best overall response was defined according to the World Health Organization tumor measurement and response criteria as the best response recorded from the start of treatment until disease progression or surgery. Confirmation of response by additional imaging was not requested.

Patients were followed up until the end of treatment visit (scheduled within 30 days after surgery, or after stop of trial medication for patients not undergoing surgery), and no data were collected after the end of treatment visit.

Adverse event reporting

Adverse events (AEs) were reported once per cycle from the first dose of trial medication until 30 days after all discontinuation of trial medication, regardless of whether they were considered related to a medication. The highest grade observed in a cycle was documented. Targeted AEs were limited to neutrophil count decreased, febrile neutropenia, anemia, platelet count decreased, nausea, diarrhea, thromboembolic event, infections, skin and cutaneous disorders, left ventricular systolic dysfunction, hypertension, ejection fraction decreased, hepatobiliary disorder and interstitial lung disease/pneumonitis. Targeted AEs of any grade were documented. Non-target AEs were documented if they were grade $\geq$3 or grade 2 requiring relevant medical intervention. Severity and causality of the AEs were classified according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Event (CTCAE) version 5.

Samples and RNA-sequencing

Mandatory submission of formalin-fixed paraffin-embedded tumor tissue from the pre-treatment biopsy was sent to the IBCSG Central Pathology Office in Milan, Italy, for biobanking. The methods for RNA-sequencing (RNA-seq) are reported in Supplementary Methods, available at https://doi.org/10.1016/j.annonc.2025.10.016.

Statistical considerations

The primary objective was to explore the interaction between the RBsig status (high or low, as determined from RNA-seq data on the pre-treatment biopsy) and treatment activity, assessed by pCR.

Secondary objectives included estimating bpCR, objective response and AEs according to CTCAE version 5. Prespecified correlative objectives included translational analyses for potential factors predictive of response to randomized treatments.

On the basis of simulations, an assessable sample size of 120 patients with successful RBsig results was determined to provide 86% power for the test of treatment-by-RBsig interaction (two-sided $\alpha = 0.05$). For 110 patients the power was estimated to be 80%. The hypothesized palbociclib + letrozole + HP versus paclitaxel + HP pCR odds ratios (ORs) were set to 0.111 in RBsig-high and 2.429 in RBsig-low groups. Overall pCR was expected to be 26%. Accounting for 20% potential sample loss due to non-assessable RBsig status, the study planned to enroll 144 patients.

The number and percentages of patients in treated and assessable populations who achieved pCR and bpCR, as well as of those in the treated population who had documented grade 3+ targeted and/or other AEs, are reported with exact binomial 95% confidence intervals (CIs).

Methods for the RBsig calculations are reported in Supplementary Methods, available at https://doi.org/10.1016/j.annonc.2025.10.016. The RBsig score in pre-treatment biopsies was dichotomized at the median. Logistic regression was fitted with binary pCR values as response and treatment group, dichotomized RBsig score and their interaction as predictors. RBsig-by-treatment interaction was tested, and ORs with 95% CIs for palbociclib + letrozole + HP versus paclitaxel + HP according to RBsig are reported.

For the exploratory analyses of PAM50 subtypes, reads per kilobase per million values were derived from TMM-normalized STAR counts. PAM50 subtypes were assigned using the absolute intrinsic molecular subtyping (AIMS) method,[20] as implemented in the R package AIMS (version 1.40.0). Association of PAM50 subtypes with treatment response was assessed using logistic regression as described in the preceding text. Overall pCR OR between luminal and non-luminal subtypes was estimated using logistic regression refitted without interaction term.

RESULTS

Patient population

Between April 2019 and July 2022, 147 patients were randomly assigned. The treated population consisted of 145 patients, 74 assigned to paclitaxel + HP and 73 to palbociclib + letrozole + HP (Figure 1, CONSORT diagram). This population consisted primarily of older postmenopausal women, with 68.2% of the participating patients being >65 years and 20.0% being ≥75 years (Table 1). Of the 101 patients >65 years, 66 (65.3%) had a G8 score >14, indicating a better health status and no potential indication for comprehensive geriatric assessment. More than 60% of the participating women had cT2 tumors and 75% had no nodal involvement at diagnosis (cN0); 56.3% of the tumors were of high grade (grade 3).

Treatment exposure

In the treated population, five cycles of trastuzumab and pertuzumab were completed by 95.2% of the patients (93.2% in the paclitaxel + HP group and 97.2% in the palbociclib + letrozole + HP group). The 12-weekly administrations of paclitaxel were completed by 79.5% of the patients, with 15 patients (20.5%) discontinuing treatment early [12 due to AEs: infusion reaction ($n = 5$), grade 2-3 neuropathy ($n = 3$), other AEs ($n = 4$)]. Four cycles of palbociclib were completed by 94.4% of the patients, with four patients discontinuing treatment early [two due to AEs: grade 3 alanine aminotransferase (ALT)/aspartate aminotransferase (AST) increase] (Table 2). No patients discontinued treatment due to disease progression.

Safety

In the treated population, grade 3-4 targeted and non-targeted AEs were reported in 23 patients (31.5%) in the paclitaxel + HP group and in 39 patients (54.2%) in the palbociclib + letrozole + HP group, consisting primarily of uncomplicated neutropenia (6.9% and 43.1% in the paclitaxel + HP and the palbociclib + letrozole +HP groups, respectively). The incidence of grade 3 diarrhea was 11.0% and 8.3% in the paclitaxel + HP and the palbociclib + letrozole + HP groups, respectively. Three cases of grade 3-4 left ventricular systolic dysfunction [one (1.4%) in the paclitaxel + HP group and two (2.9%) in the palbociclib + letrozole + HP group] and one case (1.4%) of ejection fraction decreased in the paclitaxel + HP group were reported. Among grade 3 non-targeted AEs, peripheral sensory neuropathy was reported in three patients (4.1%) in the paclitaxel + HP group only, while increases in AST, ALT and bilirubin were reported in one patient each (1.4%) in the paclitaxel + HP group and in three (4.1%), three (4.1%) and one (1.4%) patients, respectively, in the palbociclib + letrozole + HP group (Table 2 and Supplementary Table S1A and B, available at https://doi.org/10.1016/j.annonc.2025.10.016)

Efficacy

Surgery was carried out in 98.6% of the patients in the treated population [97.3% (71/73) in the paclitaxel + HP group and 100% (72/72) in the palbociclib + letrozole + HP group]. This consisted of breast-conserving surgery in 74.5% of patients (67.1% in the paclitaxel + HP group and 81.9% in the palbociclib + letrozole + HP group). Exclusive sentinel lymph node biopsy was the most frequent axillary surgical procedure (63.0% in the paclitaxel + HP group and 79.2% in the palbociclib + letrozole + HP group)

Table 1. Baseline clinical and pathological characteristics in the treated population

Characteristic	Paclitaxel + HP $n = 73$ n (%)	Palbociclib + letrozole + HP $n = 72$ n (%)	Overall $N = 145$ n (%)
Age at randomization, years, median (IQR)	69 (64-74)	69 (59-72)	69 (63-73)
<65	21 (28.8)	25 (34.7)	46 (31.7)
65-74	34 (46.6)	36 (50.0)	70 (48.3)
75-85	17 (23.3)	11 (15.3)	28 (19.3)
>85	1 (1.4)	0 (0.0)	1 (0.7)
Age and G8 score[a]			
<65 years	21 (28.8)	25 (34.7)	46 (31.7)
≥65 years and G8 score ≤14	19 (26.0)	15 (20.8)	34 (23.4)
≥65 years and G8 score >14	33 (45.2)	32 (44.4)	65 (44.8)
Clinical node involvement[a]			
cN0	54 (74.0)	55 (76.4)	109 (75.2)
cN1	19 (26.0)	17 (23.6)	36 (24.8)
Tumor size (radiological)			
cT1c	23 (31.5)	18 (25.0)	41 (28.3)
cT2	44 (60.3)	50 (69.4)	94 (64.8)
cT3	6 (8.2)	2 (2.8)	8 (5.5)
Unknown	0 (0.0)	2 (2.8)	2 (1.4)
ECOG PS			
0: fully active	65 (89.0)	67 (93.1)	132 (91.0)
1: restricted in physical activity	8 (11.0)	5 (6.9)	13 (9.0)
Dominant histological type			
Invasive ductal carcinoma NST	69 (94.5)	61 (84.7)	130 (89.7)
Invasive lobular	2 (2.7)	8 (11.1)	10 (6.9)
Other/not specified	2 (2.7)	3 (4.2)	5 (3.4)
Grade			
Grade 1	4 (6.0)	3 (4.4)	7 (5.2)
Grade 2	26 (38.8)	26 (38.2)	52 (38.5)
Grade 3	37 (55.2)	39 (57.4)	76 (56.3)
Missing/not evaluated	6	4	10
Ki67 %, median (IQR)	30 (20-40)	30 (20-40)	30 (20-40)
ER positive (≥10%)	73 (100)	72 (100)	145 (100)
PgR positive (≥1%)	57 (78.1)	55 (76.4)	112 (77.2)
HER2 status			
IHC 2+ and FISH amplified	23 (31.5)	18 (25.0)	41 (28.3)
IHC 3+	50 (68.5)	54 (75.0)	104 (71.7)

ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HP, trastuzumab + pertuzumab; IHC, immunohistochemistry; IQR, interquartile range; NST, no special type; PgR, progesterone receptor.

(Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2025.10.016).

In the treated population, the pCR rate was 32.9% (95% CI 22.3% to 44.9%) in the paclitaxel + HP group and 33.3% (95% CI 22.6% to 45.4%) in the palbociclib + letrozole + HP group; three additional patients had pCR in the breast only, resulting in similar estimates for bpCR. A best overall response of complete response + partial response by clinical or radiological assessment before surgery was reported in 44 patients (60.3%, 95% CI 48.1% to 71.5%) in the paclitaxel + HP group and in 47 patients (65.3%, 95% CI 53.1% to 76.1%) in the palbociclib + letrozole + HP group (Table 3).

RBsig evaluation and primary objective

RBsig was successfully assessed by RNA-seq on 118 pre-treatment biopsy samples. After excluding 3 patients in the paclitaxel group who did not receive a full dose of treatment in the first cycle (Figure 1), the assessable population for the primary objective was composed of 115 patients (58 in the paclitaxel + HP group and 57 in the palbociclib + letrozole + HP group). The clinical and pathological characteristics of this population were similar to those of the treated population (Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2025.10.016). The median pre-treatment RBsig score was 45 [interquartile range (IQR) 18-74] in the paclitaxel + HP group and 33 (IQR 1-55) in the palbociclib + letrozole + HP group (Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2025.10.016). In the assessable population, the pCR rate was 36.2% (95% CI 24.0% to 49.9%) in the paclitaxel + HP group and 31.6% (95% CI 19.9% to 45.2%) in the palbociclib + letrozole + HP group. pCR rates by RBsig status were similar across groups (Figure 2A). In logistic regression analysis, RBsig-by-treatment interaction was not statistically significant (OR 2.90, 95% CI 0.61-14.10, $P = 0.18$), indicating similar frequencies of response for palbociclib + letrozole + HP versus paclitaxel + HP between RBsig-low (OR 0.5, 95% CI 0.2-1.4) and RBsig-high (OR 1.4, 95% CI 0.5-4.1) subgroups.

PAM50 exploratory analysis

In the assessable population, the most frequent PAM50 subtype was HER2-enriched (48.7%), followed by luminal B

Table 2. Treatment exposure and targeted or other adverse events

	Paclitaxel + HP $n = 73$ n (%)	Palbociclib + letrozole + HP $n = 72$ n (%)
Treatment exposure		
Paclitaxel		
Completed four cycles of treatment	58 (79.5)	—
Early discontinuation due to AE[a]	12 (16.4)	—
Early discontinuation due to other reasons	3 (4.1)	
Palbociclib		
Completed four cycles of treatment	—	68 (94.4)
Early discontinuation due to AE[b]	—	2 (2.8)
Early discontinuation due to other reason		2 (2.8)
Trastuzumab + pertuzumab		
Completed five doses of treatment	68 (93.2)	70 (97.2)
Early discontinuation due to AE	5 (6.8)	1[c] (2.8)
Patients with targeted or other AEs of grade 3 or 4 (CTCAE version 5)		
Event type		
Targeted[d] (95% CI, %)	15 (20.5) (12.0-31.6)	38 (52.8) (40.7-64.7)
Other[e] (95% CI, %)	12 (16.4) (8.8-27.0)	5 (6.9) (2.3-15.5)
Combined (95% CI, %)	23 (31.5) (21.3-43.4)	39 (54.1) (42.0-66.0)

Reasons for early discontinuation: paclitaxel: AE: infusion reaction ($n = 5$), grade 2-3 neuropathy ($n = 3$), other AE ($n = 4$); other reasons: COVID ($n = 1$), patient's/physician's decision ($n = 2$); palbociclib: AE: grade 3 ALT/AST increase ($n = 2$); other reasons: COVID ($n = 1$), surgeon's decision ($n = 1$).
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; COVID, coronavirus disease; CTCAE, Common Terminology Criteria for Adverse Events; HP, trastuzumab + pertuzumab.
[a]Five out of 12 patients did not receive first full dose of paclitaxel due to infusion reactions ($n = 4$) and grade 3 muscle cramp ($n = 1$).
[b]There were no discontinuations during the first cycle.
[c]One additional patient skipped one dose of pertuzumab due to grade 3 diarrhea.
[d]Targeted AEs: neutrophil count decreased, febrile neutropenia, anemia, platelet count decreased, nausea, diarrhea, thromboembolic event, infections, skin and cutaneous disorders, left ventricular systolic dysfunction, hypertension, ejection fraction decreased, hepatobiliary disorder, interstitial lung disease/pneumonitis.
[e]Other (non-targeted) AEs are collected as grade ≥2—but only grade 2 AEs that required relevant medical intervention were to be reported.

(27.8%) (Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2025.10.016). RBsig levels were highest in the HER2-enriched and basal subtypes, and the lowest in the luminal A and normal-like groups (Supplementary Figure S2, available at https://doi.org/10.1016/j.annonc.2025.10.016). When aggregated in two subgroups (luminal and non-luminal), the pCR rate was higher in the non-luminal subgroup: 45.5% (95% CI 33.1% to 58.2%) compared with 18.4% (95% CI 8.8% to 32.0%) in the luminal subgroup. There was no evidence of a difference in treatment effect between luminal and non-luminal status (OR 0.68, 95% CI 0.11-3.90, $P = 0.66$; Figure 2B).

DISCUSSION

ER-positive/HER2-positive BC represents a subset of HER2-positive disease with particular biological and clinical features. Compared with ER-negative/HER2-positive tumors, ER-positive/HER2-positive tumors display lower HER2 levels and are less likely to be HER2-enriched by PAM50,[21] therefore showing lower pCR rates upon anti-HER2 therapy, even in combination with CT. Additionally, when compared with ER-positive/HER2-negative tumors, ER-positive/HER2-positive tumors are more endocrine resistant.[21] Biologically, these features are explained by the bi-directional cross-talk between the ER and HER2 pathways. The HER2

Table 3. Best overall response and pCR in the treated population

	Paclitaxel + HP $n = 73$ n (%)	Palbociclib + letrozole + HP $n = 72$ n (%)	Overall $N = 145$ n (%)
Best overall response			
CR	15 (20.5)	17 (23.6)	32 (22)
PR	29 (39.7)	30 (41.7)	59 (40.7)
SD	14 (19.2)	16 (22.2)	30 (20.7)
PD	3 (4.1)	2 (2.8)	5 (3.4)
NE	12 (16.4)	7 (9.7)	19 (13.1)
Pathological complete response			
pCR in breast only (95% CI, %)	26 (35.6) (24.7-47.7)	25 (34.7) (23.9-46.9)	51 (35.2) (27.4-43.5)
pCR (95% CI, %)	24 (32.9) (22.3-44.9)	24 (33.3) (22.6-45.4)	48 (33.1) (25.5-41.4)

CI, confidence interval; CR, complete response; NE, not evaluable; pCR, pathological complete response; PD, progressive disease; PR, partial response; SD, stable disease;

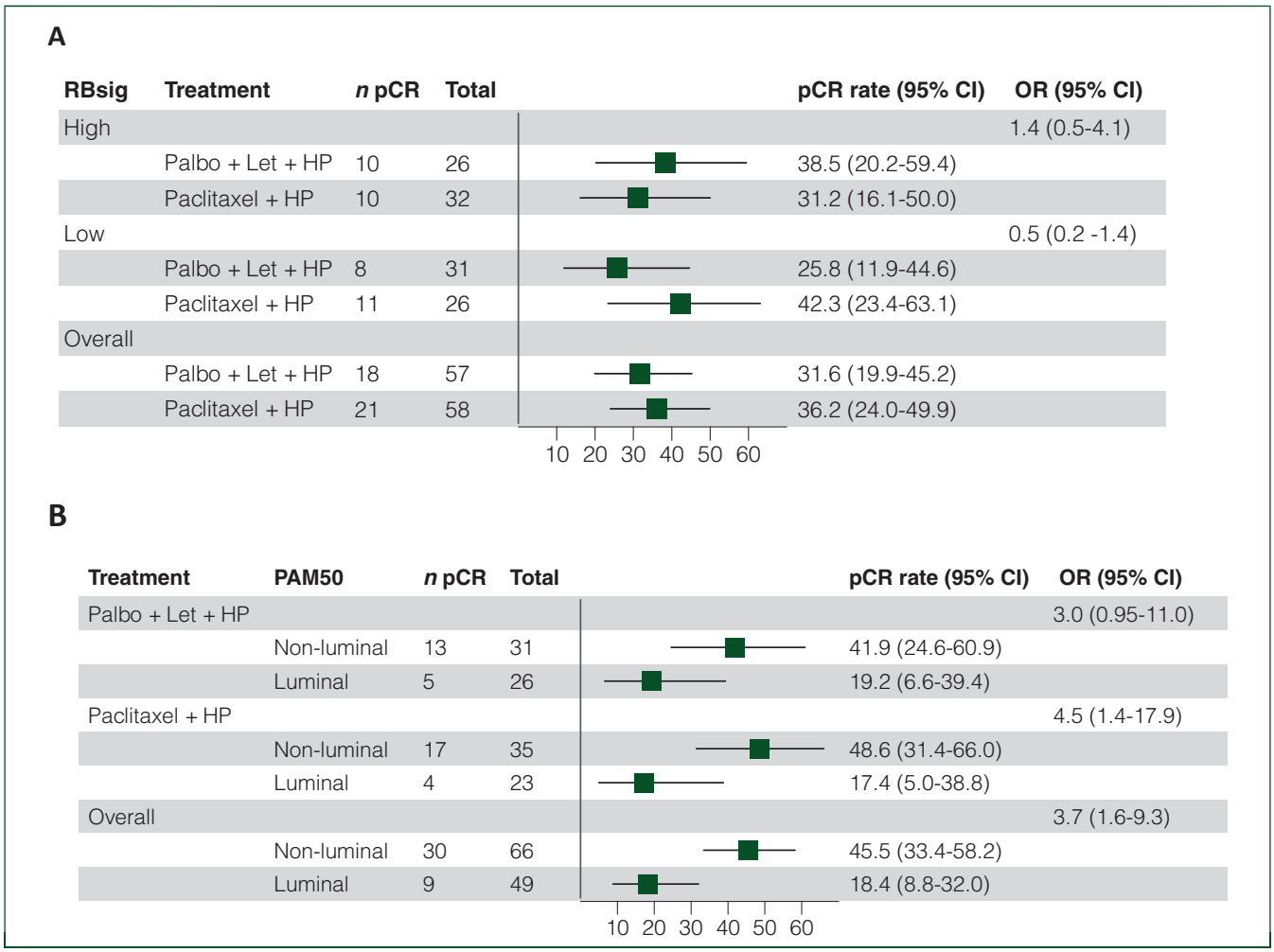


Figure 2. pCR by RBsig and PAM50. pCR by pre-treatment biopsy RBsig score (A) or PAM50 subtype (B) and treatment group in the assessable population. RBsig-by-treatment interaction OR 2.90, 95% CI 0.61-14.10, *P* value for the interaction test = 0.18.
CI, confidence interval; HP, trastuzumab + pertuzumab; Let, letrozole; OR, odds ratio; Palbo, palbociclib; pCR, pathological complete response.

pathway alters ER function and its transcriptional activity favoring endocrine resistance. In turn, ER inhibits HER2 expression, functioning as an alternative survival pathway upon HER2 blockade and contributing to anti-HER2 therapy resistance.[22] In patients with ER-positive/HER2-positive BC, combinations of ET and anti-HER2 therapies without CT have shown activity both in the early and the metastatic settings.[23,24] In the neoadjuvant setting, however, dual anti-HER2 blockade (with trastuzumab + either lapatinib[25-27] or pertuzumab[28]) with ET has achieved low pCR rates of ~20%. Pre-clinical and clinical data have shown that the CDK4/6 pathway is crucial in the biology of ER-positive/HER2-positive BCs and that treating these tumors with triplets of ET, CDK4/6 inhibitors and anti-HER2 therapy may be an option to avoid CT.[29,30] This approach would be of particular value in subgroups of elderly or frail patients who may not tolerate well the side-effects of CT. However, given the heterogeneity of ER-positive/HER2-positive tumors, it is currently unknown how to select patients who may forego CT in favor of an endocrine treatment plus a CDK4/6 inhibitor, in combination with anti-HER2 agents.

TOUCH was originally designed to address an older patient population (≥65 years). Elderly patients are traditionally poorly represented in clinical trials and can therefore be considered as a group with an unmet clinical need.[31] This led to the decision to use two different de-escalated treatment regimens in each randomized group. In particular, the schedule of weekly paclitaxel at a dose of 80 mg/m^2 on days 1, 8 and 15 every 28 days was chosen to reduce treatment burden and risk of toxicity by allowing a week off treatment.[32] Compared with other de-escalation studies in this setting[28] where a weekly paclitaxel schedule with no interruptions was used for a total duration of 12 weeks, our study allowed patients to receive the same cumulative dose of paclitaxel (12 administrations) over a longer treatment period (16 weeks), which permitted an additional administration of HP (five cycles in total). This schedule was maintained even after the protocol was amended to allow the inclusion of postmenopausal women with no age indications. Ultimately, the study population consisted primarily of older postmenopausal women, with a good representation of

patients >75 years. These represent unique features of the TOUCH trial which may inform future studies in this setting.

The results of TOUCH show that a de-escalated, CT-free approach using letrozole and palbociclib for 16 weeks achieves a pCR rate of 33% in molecularly unselected patients with ER-positive/HER2-positive early BC, when combined with dual anti-HER2 blockade with trastuzumab and pertuzumab. This result was superior to the expected pCR rate in this population (20%), but compares well with two single-arm trials investigating the association of ET, dual anti-HER2 blockade and CDK4/6 inhibition (NAPHER-2, six cycles of HP + palbociclib + fulvestrant: pCR 27%[33]; MUKDEN-01, five cycles of pyrotinib, dalpiciclib and letrozole: pCR 30.4%[34]). Indirect comparison of these data with the low pCR rates obtained in trials exploring the use of anti-HER2 therapy in combination with ET alone[25,26,28] indeed highlights that the addition of CDK4/6 inhibitors may be an effective strategy to increase the efficacy of ET in this population. Notably, although grade 3 and 4 AEs were common in this arm, they consisted mainly of uncomplicated neutropenia. Overall, the toxicity profile of the combination of palbociclib + letrozole and HP was in line with the safety data for these agents and treatment discontinuations due to AEs were remarkably low.

In TOUCH, the availability of a de-escalated CT arm with weekly paclitaxel allows for further considerations. In this group, the pCR rate was 33%, which also compares well with similar combinations of taxanes and dual anti-HER2 blockade.[4,28,29,35] As most of these trials allowed the inclusion of patients with higher-risk BC (T4 and/or N2-3),[35] this is of particular interest as TOUCH included patients with comparatively more limited disease (cT1c-T3 and cN0-N1). In this treatment group, however, compliance was lower as compared with the palbociclib + letrozole + HP group, with more discontinuations due to AEs.

TOUCH was designed based on previous observations, derived from retrospective analyses, that a gene signature of E2F pathway activity and *RB1* loss of function (RBsig) was associated with both sensitivity to CT and resistance to CDK4/6 inhibitors in different BC settings.[15,16,36] Therefore, we hypothesized that palbociclib in combination with dual anti-HER2 blockade and ET may be an effective neoadjuvant therapy for ER-positive/HER2-positive BC, especially in the subset of tumors with low RBsig. We also hypothesized that tumors with high RBsig might be particularly sensitive to neoadjuvant CT with paclitaxel and dual anti-HER2 blockade. The primary study hypothesis was not proven by the data and did not show any interaction between RBsig and study treatment, with pCR rates being similar across the RBsig spectrum. This might be due to differences between the study population of prior retrospective studies of RBsig in BC and TOUCH. Here, a more selected group of older postmenopausal patients deemed suitable for a de-escalated treatment was included, potentially enriching the study with less aggressive tumors. Additionally, in the assessable population of patients with available RNA-seq data, the pCR rates were slightly skewed in the two treatment groups, favoring the paclitaxel group (36.2% versus 31.6%). Median RBsig score at baseline was also higher in the paclitaxel group. Whether these aspects might have impacted on the possibility of detecting a predictive signal for RBsig in TOUCH is unclear. As expected, RBsig was differently expressed across the PAM50 BC subtypes with the highest levels observed in the HER2-enriched samples and the lowest in the luminal samples. Of note, PAM50 status did not show any interaction with treatment, suggesting that it cannot be used as a predictive biomarker in this setting. However, it is notable that HER2-enriched tumors had the highest pCR rates in both treatment groups which was close to 50%. This may be due to the well-known sensitivity of this subtype to dual anti-HER2 blockade irrespective of the treatment backbone.[37] On the other hand, luminal subtypes had a pCR rate of 18% in the palbociclib + letrozole + HP group, which is comparatively higher than other trials not incorporating a CDK4/6 inhibitor,[25,28] which may suggest that palbociclib partially restores endocrine sensitivity in these tumors. These data highlight the complex interplay between ER-positive/HER2-positive BC heterogeneity and treatment response, supporting current research efforts in novel biomarker testing in this setting.[35]

This trial has several limitations. TOUCH was powered to detect a significant interaction between RBsig status and treatment; however, the limited sample size of the study does not allow for direct comparisons between the two groups either in terms of efficacy or toxicity. Also, the trial treatment duration was identical between the two groups (16 weeks) to allow for an equal exposure to dual anti-HER2 therapy. However, TBCRC023 has shown that chemo-free approaches in this population might obtain numerically higher pCR rates if treatment is extended up to 24 weeks.[27] Given the good tolerability of the palbociclib + letrozole + HP combination, this might be a viable option for future studies. Another limitation of the trial is the absence of quality of life and long-term follow-up data, as no patient-reported outcomes were recorded and patients were followed up only until surgery. Additionally, after surgery, any further therapy was eventually chosen by the treating physician and not recorded. From a biomarker perspective, TOUCH did not archive blood samples for liquid biopsy and did not collect on-treatment tissue biopsies to study the dynamics of molecular changes associated with response, which may help identify clinically relevant biomarkers.[38] However, the RNA-seq dataset is available from both pre-treatment biopsies and surgical samples and additional molecular analyses are ongoing to study the biology of ER-positive/HER2-positive disease and the potential impact of novel biomarkers.

In conclusion, TOUCH has shown that a CDK4/6 inhibitor in combination with ET and dual anti-HER2 blockade, without CT, achieves a pCR in one-third of ER-positive/HER2-positive patients with good tolerability. Molecular classification based on RBsig or PAM50 was not useful to identify patients with differential benefit from either

treatment regimen. These promising results with a CT-free regimen warrant further consideration in larger prospective clinical trials.

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DISCLOSURE

LM reports receiving honoraria from Pfizer, Novartis and Seagen; serving as a consultant or advisor for AstraZeneca, Pfizer, Novartis, Lilly, Seagen, Roche and Menarini; receiving research grant support (to institution) from Pfizer and Novartis; and receiving travel, accommodation and/or other travel-related support from Roche, Janssen, Gilead Sciences, Novartis and Menarini. AG reports serving on an advisory board (fees to institution) for AstraZeneca, Seagen and Lilly; receiving travel grant support (to institution) from AstraZeneca, Daiichi Sankyo, Gilead, Lilly and Novartis; and receiving speaker fees (to institution) from Daiichi Sankyo, Lilly, Novartis, MSD and Roche. MC reports receiving research grant funding from Roche (to institution) and serving as the Co-Chair of the International Breast Cancer Study Group Scientific Committee. AM reports receiving travel grant support from Roche and Pfizer; serving as a consultant for Roche; and serving as a paid consultant/providing expert testimony (personal payment) for Novartis. AMM reports serving on an advisory board for Novartis, Pierre Fabre, MSD, Regeneron, BMS, Genomic Health, AstraZeneca, Daiichi Sankyo and Pfizer; receiving fees for invited speeches from Novartis, Pierre Fabre, MSD, Merck, Sun Pharma and Regeneron; receiving travel grant support from Pierre Fabre, Gilead and Pfizer; and receiving an educational grant from Pfizer. DT reports serving as a consultant for Novartis, Lilly and Roche; receiving honoraria from Novartis; and receiving travel grant support from Novartis and Lilly. EG reports receiving travel grant support from Roche, Daiichi Sankyo, Pfizer and Novartis, and serving on an advisory board for Roche, Daiichi Sankyo, Pfizer and Novartis. AF reports receiving travel grant support from Novartis, Lilly, Pfizer, Gilead and MSD, and serving on an advisory board for Novartis, Lilly, Pfizer, Gilead and MSD. GV reports serving on advisory boards (personal payments) for AstraZeneca, Daiichi Sankyo, MSD Oncology, Pfizer and Roche; receiving consulting fees from Agilent; serving as an invited speaker for Gilead; receiving research grant support (to institution) from Roche; receiving funding support (to institution) as a coordinating principal investigator for AstraZeneca; and receiving support (personal payment) for an educational webinar from Medscape. SL reports receiving research funding (payments to institution) from Novartis, Bristol Myers Squibb, MSD, Pfizer, Eli Lilly, Nektar Therapeutics, Gilead Sciences, AstraZeneca/Daiichi Sankyo and Roche-Genentech; reports serving as a consultant (paid and unpaid) to Novartis, Bristol Myers Squibb, MSD, AstraZeneca/Daiichi Sankyo, Eli Lilly, Amaroq Therapeutics, Mersana Therapeutics, Domain Therapeutics, BioNTech, Bicycle Therapeutics, Exact Sciences, Menari Asia-Pacific, SAGA Diagnostics, Gilead Sciences, Roche-Genentech and Adanate; receiving payment of honoraria for speaking at educational events from Novartis, MSD, Gilead Sciences, Exact Sciences, Roche-Genentech and AstraZeneca; receiving support for attending meetings and/or travel (payments to institution) from BMS and Roche-Genentech; as well as reports serving as the Co-Chair for the International Breast Cancer Study Group (IBCSG) Scientific Committee. MMR reports receiving grant support (to institution) from BMS, Biotheranostics, Novartis, Pfizer and Roche (outside submitted work), and personal fees from BMS and Tolmar (outside submitted work). LB reports receiving honoraria (and/or consultant or advisory fees) from Amgen, AstraZeneca, Boehringer-Ingelheim, Daiichi Sankyo, Eisai, Exact Sciences, Gilead, Lilly, Menarini, MSD, Novartis, Pfizer Pierre Fabre, Roche, Sanofi and Seagen; receiving grant support (to institution) from Celgene, Genomic Health and Novartis; and receiving travel grant support from AstraZeneca, Daiichi Sankyo and MSD. All other authors have declared no conflicts of interest.

DATA SHARING

After publication, access to deidentified participant data may be requested by researchers by submitting a proposal (to stat_center@ibcsg.org), which will be reviewed for scientific merit and feasibility in accordance with the Guidelines for Collaborative Research (https://www.ibcsg.org/images/Member/Publi/Documents/Guidelines_for_Collaborative_Research_for_ETOP_IBCSG_Partners_Foundation_Dec_2022.pdf) and data sharing policy (https://www.ibcsg.org/images/

Member/Publi/Documents/Data_Sharing_Policy_for_IBCSG_Trials_Dec_2022.pdf) for IBCSG trials.

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