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SHORT COMMUNICATION

Palbociclib and trastuzumab for HER2-positive metastatic breast cancer: final overall survival results of cohort A and B of SOLTI-1303-PATRICIA trial

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Background: The SOLTI-1303-PATRICIA trial (NCT02448420) is a phase II study investigating palbociclib and trastuzumab, with or without endocrine therapy, in hormone receptor (HR)-positive/human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer (MBC). This manuscript presents final overall survival (OS) results and biomarker analyses.

Patients and methods: Patients previously treated with trastuzumab and two to four regimens were eligible. For estrogen receptor (ER)-negative disease (cohort A), patients received palbociclib and trastuzumab. For ER-positive disease, patients were randomized 1 : 1 to cohort B1 (no additional therapy) or B2 (letrozole). OS and long-term progression-free survival (PFS) were pre-defined secondary endpoints. Kaplan—Meier curves and stratified Cox models were used.

Results: Among 71 patients, median OS was 29.8 months [95% confidence interval (CI) 20.9-38.0 months]; 4-year OS rates were 13.3% (A), 35.7% (B1), and 32.3% (B2). PAM50 luminal subtypes showed better OS than non-luminal subtypes (38.0 versus 26.6 months). Exploratory biomarker analyses found luminal-related genes associated with better long-term survival, while basal and proliferation-related genes were linked to resistance. Higher luminal A, luminal B, and previously reported chemo-endocrine scores correlated with favorable prognoses.

Conclusions: These findings highlight the relevance of gene expression profiling in HER2-positive breast cancer and support biomarker-driven patient selection. Long-term PATRICIA results validate the potential of non-chemotherapy-based approaches in HR-positive/HER2-positive MBC.

Key words: metastatic breast cancer, HR-positive/HER2-positive, palbociclib, trastuzumab, biomarkers, gene expression profiling

INTRODUCTION

The advent of anti-human epidermal growth factor receptor 2 (HER2) therapies has significantly improved survival in HER2-positive metastatic breast cancer (MBC), yet the disease remains incurable, with long-term survivors requiring multiple lines of therapy.[1-4] This highlights the need for innovative, well-tolerated strategies to improve outcomes and quality of life.

Combining cyclin-dependent kinases 4/6 (CDK4/6) inhibitors with anti-HER2 therapies offers a promising approach

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for hormone receptor (HR)-positive/HER2-positive MBC. Emerging data from recent clinical trials show that combining CDK4/6 inhibitors, such as palbociclib or abemaciclib, with anti-HER2 agents offers promising results, particularly in extending progression-free survival (PFS). The MonarcHER trial demonstrated improved PFS with abemaciclib, trastuzumab, and fulvestrant compared with trastuzumab and chemotherapy.[5,6] Similarly, the PATRICIA trial cohorts A and B highlighted the efficacy and safety of palbociclib with trastuzumab in PAM50 luminal HR-positive/HER2-positive MBC.[7] Based on these results, a new cohort was later added to test the hypothesis that palbociclib, trastuzumab, and endocrine therapy (ET) offer superior outcomes compared with the physician's treatment of choice in HER2-positive/estrogen receptor (ER)-positive and PAM50 luminal disease.[8] Recently, the phase III PATINA trial further supported this strategy, reporting significantly extended PFS with palbociclib added to first-line maintenance therapy, with patients achieving a median PFS of 44.3 months compared with 29.1 months for those treated with anti-HER2 and ET alone.[9]

Here, we present the final overall survival (OS) analysis from cohorts A and B of the PATRICIA trial, along with updated PFS data and biomarker analysis, to further characterize the long-term prognosis of patients with MBC treated with a combination of CDK4/6 inhibitors and anti-HER2 therapies.

PATIENTS AND METHODS

Patients and treatments

The SOLTI-1303-PATRICIA trial (NCT02448420) is an investigator-initiated, multicenter, open-label, phase II study conducted at 17 sites across Spain, with patient recruitment from July 2015 to November 2018. The trial followed Simon two-stage design and included three cohorts: ER-negative (cohort A) and ER-positive (cohorts B1 and B2) (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2025.105572).

Eligible participants were postmenopausal patients with HER2-positive MBC who had received prior trastuzumab and experienced documented progression disease following two to four previous regimens in the advanced setting. Patients were treated with palbociclib (200 mg daily, 2 weeks on/1 week off) and trastuzumab (8 mg/kg loading dose, then 6 mg/kg intravenously or 600 mg subcutaneously every 21 days). Dose reductions for palbociclib (to 150 mg or 100 mg) were permitted. For ER-positive disease, patients were randomized 1 : 1 to cohort B1 (no additional therapy) or cohort B2 (letrozole 2.5 mg/day).

Aims and endpoints

The primary endpoint was PFS at 6 months as assessed by investigators according to RECIST version 1.1. Secondary endpoints included OS and long-term PFS. Detailed trial design and methodology have been previously published.[7]

Biomarker analyses

Approximately 100 ng of total RNA was used to measure the expression of 55 and 192 breast cancer-related genes using two different code sets with the nCounter platform (Nanostring Technologies, Seattle, WA). Data were normalized with five housekeeping genes and log2 transformed. Intrinsic molecular subtypes were identified using the PAM50 predictor, following established methods.[1] For each sample, we calculated nine gene signatures: the correlation coefficient to the five PAM50 centroids (basal-like, HER2-enriched, luminal A, luminal B, and normal-like),[10] the PAM50 proliferation signature,[11] two PAM50 risk of recurrence models (ROR subtype and ROR proliferation), and the chemoendocrine score (CES).[12,13]

Statistical methods

Survival endpoints were estimated using the Kaplan—Meier method. Stratified univariable and multivariable Cox proportional models were used to estimate hazard ratios, using the study cohort as a stratified factor. All variables evaluated in the univariable analysis were included in the multivariable model. The median follow-up time was calculated using the reverse Kaplan—Meier method. All tests were two-sided, with no adjustment for multiple comparisons due to the exploratory nature of the analysis. No data imputation was carried out and all analyses were carried out using R statistical software version 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

A total of 71 patients were enrolled in this study: 15 in cohort A and 56 in cohort B, with cohort B evenly split between patients receiving letrozole ($n = 28$) and those not receiving letrozole ($n = 28$). The mean age of participants was 59.1 years, and the median number of prior lines of systemic therapy was three. Most patients (95.8%) had previously been treated with anti-HER2 therapies in the metastatic setting, in addition to trastuzumab (Table 1 and Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2025.105572).

At the data cut-off in November 2024, 56 deaths (78.9%) had been recorded, with a median follow-up of 60.5 months. The median OS was 29.8 months [95% confidence interval (CI) 20.9-38.0 months]: 21.5 months (95% CI 14.6-38.2 months) in cohort A, 29.5 months (95% CI 16.7-54.7 months) in cohort B1, and 33.8 months [95% CI 21.2 months-not reached (NR)] in cohort B2. At 4 years, OS rates were 13.3% in cohort A, 35.7% in cohort B1, and 32.3% in cohort B2. The updated investigator-assessed median PFS was 4.1 months (95% CI 1.8 months-NR) in cohort A, 5.9 months (95% CI 4.0-10.8 months) in cohort B1, and 5.5 months (95% CI 3.7-17.2 months) in cohort B2. PFS rates at 12 months were 15.0% in cohort A, 18.5% in cohort B1, and 28.6% in cohort B2 (Figure 1A and B).

Table 1. Baseline demographic and clinical characteristics of patients according to treatment group

Characteristic	Cohort A ($n = 15$)	Cohort B1 ($n = 28$)	Cohort B2 ($n = 28$)	Total ($n = 71$)
Age, mean (range), years	61.7 (34-81)	60.1 (41-89)	56.6 (40-82)	59.1 (34-89)
Race, *n* (%)				
Caucasian	14 (93.3)	22 (78.6)	26 (92.9)	62 (87.3)
Other	1 (6.7)	6 (21.4)	2 (7.1)	9 (12.7)
ECOG PS, *n* (%)				
0	8 (53.3)	13 (46.4)	13 (46.4)	34 (47.9)
1	7 (46.7)	15 (53.6)	15 (53.6)	37 (52.1)
Hormone receptor status, *n* (%)				
ER-positive/PgR-positive	0	21 (75.9)	16 (57.1)	37 (52.1)
ER-positive/PgR-negative	0	6 (21.4)	11 (39.3)	17 (23.9)
ER-negative/PgR-positive	0	1 (3.6)	0	1 (1.4)
ER-negative/PgR-negative	15 (100)	0	1 (3.6)	16 (22.5)
Disease extension, *n* (%)				
Metastatic	14 (93.3)	23 (82.1)	26 (92.9)	63 (88.7)
Unresectable locally advanced or recurrent	1 (6.7)	5 (17.9)	2 (7.1)	8 (11.3)
Measurable disease, *n* (%)	11 (73.3)	23 (82.1)	22 (78.6)	56 (78.9)
Visceral disease, *n* (%)	10 (66.7)	17 (60.7)	19 (67.9)	46 (64.8)
Adjuvant treatment, *n* (%)	7 (46.7)	19 (67.9)	13 (46.4)	39 (54.9)
Adjuvant trastuzumab, *n* (%)	5 (33.3)	8 (28.6)	8 (28.6)	21 (29.6)
Prior lines of therapy in metastatic setting, *n* (%)				
2	3 (20.0)	7 (25.0)	5 (17.9)	15 (21.2)
3	9 (60.0)	9 (32.1)	10 (35.7)	28 (39.4)
4	3 (20.0)	12 (42.9)	13 (46.4)	28 (39.4)
Previous exposure to HER2-directed therapy in metastatic setting, *n* (%)				
Trastuzumab	15 (100)	28 (100)	28 (100)	71 (100)
Pertuzumab	8 (53.3)	13 (46.4)	15 (53.6)	36 (50.7)
Trastuzumab emtansine	9 (60.0)	18 (64.28)	16 (57.1)	43 (60.7)
Lapatinib	7 (46.6)	17 (60.7)	12 (42.9)	36 (50.7)
Neratinib	0	3 (10.7)	3 (10.7)	6 (8.5)
Tucatinib	0	0	0	0
Trastuzumab deruxtecan	0	0	0	0
Previously treated asymptomatic brain metastasis, *n* (%)	0	0	2 (7.1)	2 (2.8)

ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PgR, progesterone receptor.

PAM50 data were available for 59 patients (83%) (Supplementary Figure S2, available at https://doi.org/10.1016/j.esmoop.2025.105572). Among these, 16.9% were classified as luminal A, 22.0% as luminal B, 49.2% as HER2-enriched, 10.2% as normal-like, and 1.7% as basal-like. Patients with luminal PAM50 subtypes[10] demonstrated significantly better long-term PFS (hazard ratio 0.48, 95% CI 0.24-0.96, $P = 0.04$) and numerically longer OS compared with those with non-luminal subtypes, although not statistically significant (median OS 38.0 versus 26.8 months, respectively) (Figure 1C and D). Associations between specific PAM50 subtypes and survival outcomes are detailed in Supplementary Figure S3, available at https://doi.org/10.1016/j.esmoop.2025.105572.

Univariable and multivariable analyses were carried out to assess the prognostic implications of clinical factors and PAM50 subtypes for PFS and OS.[10] In univariable analysis, Eastern Cooperative Oncology Group performance status, the number of prior treatment lines, and PAM50 luminal subtype were significantly associated with PFS (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2025.105572). However, in the multivariable analysis, only PAM50 luminal status remained statistically significant after adjustment for clinical variables (hazard ratio 0.44, 95% CI 0.19-0.99). In the OS multivariable analysis, patients with visceral disease had worse outcomes, while luminal subtypes showed a numerically better OS, though not statistically significant (Figure 2A).

Next, we explored the relationship between genomic signatures[10-13] and survival outcomes. Higher basal-like scores were linked to poorer outcomes, while higher luminal A, luminal B, and CES scores were associated with improved prognoses (Figure 2B). Expression of 32 of 188 genes (16.7%) was significantly associated with OS ($P < 0.05$, unadjusted). High expression of luminal-related genes, including *PGR* and *SFRP1*, correlated with better OS, while elevated expression of proliferation-related genes, such as *MELK*, *ORC6*, *UBD2C*, and *ASPM*, was associated with shorter OS. These findings underscore the prognostic importance of genomic features (Figure 2C). Associations between genes and PFS are presented in Supplementary Figure S4, available at https://doi.org/10.1016/j.esmoop.2025.105572.

DISCUSSION

The PATRICIA trial cohort A and B results reinforce the growing body of evidence supporting the combination of CDK4/6 inhibitors with anti-HER2 therapies as an effective strategy for HR-positive/HER2-positive MBC.[5,8,9,14] In the initial analysis, palbociclib combined with trastuzumab demonstrated a promising median PFS in patients with

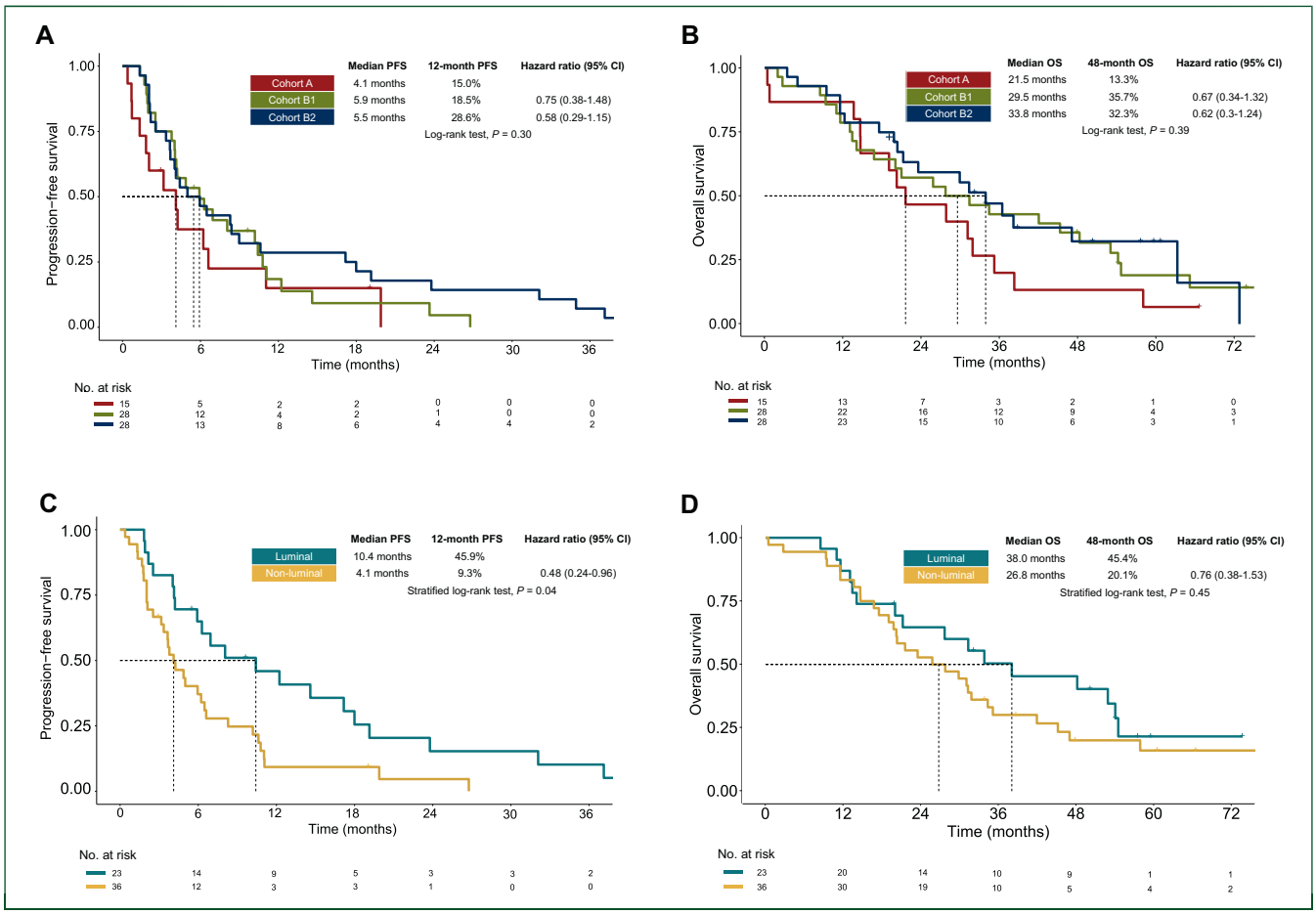

Figure 1. Association of study cohort and PAM50 luminal subtype with survival outcomes. (A) Kaplan—Meier curves with PFS outcomes in study cohorts. (B) Kaplan—Meier curves with OS outcomes in study cohorts. (C) Kaplan—Meier curves with PFS outcomes in PAM50 luminal subtype. (D) Kaplan—Meier curves with OS outcomes in PAM50 luminal subtype.
CI, confidence interval; OS, overall survival; PFS, progression-free survival.

PAM50 luminal ER-positive/HER2-positive MBC. At that time, OS data were immature. In this final analysis, median OS reached 38.0 months for patients with luminal tumors compared with 26.8 months for those with non-luminal tumors, emphasizing the prognostic value of intrinsic subtypes. These findings align with other studies, such as MonarcHER, which reported superior outcomes for luminal subtypes treated with abemaciclib-based regimens.[5]

Exploratory genomic analyses from the PATRICIA trial further revealed that luminal-related genes and signatures correlated with improved survival, while basal and proliferation-associated signatures were linked to resistance. Based on this evidence, a new study within the PATRICIA trial umbrella (cohort C) was subsequently designed to evaluate whether the combination of palbociclib, trastuzumab, and ET outperformed the treatment of physician's choice (TPC) in HER2-positive/ER-positive PAM50 luminal tumors. In this cohort, patients in the TPC arm received trastuzumab emtansine (39.4%), trastuzumab combined with chemotherapy (48.5%), or trastuzumab combined with ET (12.1%). Results from cohort C demonstrated a significant improvement in PFS for the experimental arm compared with TPC (PFS hazard ratio 0.52).[8] These findings highlight the potential of biomarker-driven patient selection and underscore the importance of translational analyses in other trials using similar combinations, such as the PATINA trial, which recently confirmed the benefit of adding palbociclib to maintenance therapy with ET and trastuzumab following induction chemotherapy in the first-line treatment of HR-positive/HER2-positive MBC.[9]

While promising, these findings must be interpreted with caution due to certain limitations. The single-arm design of the study introduces potential bias. Moreover, the observed survival difference between luminal and non-luminal subtypes may be attributable to inherent prognosis differences between these subtypes, rather than the treatment itself. The study design did not allow for a direct comparison between palbociclib with trastuzumab alone versus its combination with ET or the combination of ET with trastuzumab, making it difficult to isolate the individual contribution of ET or palbociclib. While PAM50 profiling provided valuable insights into subtype-specific responses, biomarker data were not available for all participants, limiting the generalizability of the results. Additionally, the biomarker analysis should be considered exploratory, as no correction for multiple testing was carried out. Furthermore, after the design and enrolment of the trial, the HER2-positive MBC therapeutic algorithm has changed with

Figure 2. Multivariable models, genomic and gene expression analysis. (A) Multivariable Cox models with clinical factors and PAM50 subtypes in terms of PFS and OS. (B) Association between genomic signatures as continuous scores and survival outcomes (PFS and OS). (C) Volcano plot showing the association between individual genes and OS.
CI, confidence interval; ER, estrogen receptor; OS, overall survival; PFS, progression-free survival; ROR, risk of recurrence.

emerging treatment options such as trastuzumab deruxtecan and tucatinib that have demonstrated superior efficacy. Despite these limitations, the PATRICIA trial underscores the potential of non-chemotherapy-based approaches in heavily pretreated patients, offering a less toxic alternative to standard regimens.

In conclusion, the PATRICIA trial validates the efficacy of combining palbociclib with trastuzumab and ET in this challenging patient population. Future research should focus on refining biomarker-driven strategies and exploring the integration of novel agents with CDK4/6 inhibitors to further improve outcomes for HR-positive/HER2-positive MBC.

DISCLOSURE

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DATA SHARING

The datasets generated and analyzed during this study are available from the corresponding authors upon reasonable request.

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