Corresponding author's email: antonio.llombart@medsir.org

Neoadjuvant letrozole plus palbociclib in patients with hormone receptor-positive/HER2-negative early breast cancer with baseline Ki67 ≥20% and an Oncotype DX Breast Recurrence Score® result ≥18: DxCARTES

Antonio Llombart-Cussac [1], Ángel Guerrero-Zotano [2], Manuel Ruiz [3], Begoña Bermejo [4], Miguel Gil-Gil [5], Juan de la Haba [6], Emilio Alba [7], Vanesa Quiroga [8], Vicente Carañana [9], Ander Urruticoechea [10], Serafín Morales [11], Meritxell Bellet [12], Antonio Antón [13], José Manuel Pérez-García [14], María Fernández-Abad [15], Sonia Servitja [16], Pedro Sánchez-Rovira [17], Sofia Braga [18], Miguel Sampayo [19], Andrea Malfettone [19], Javier Cortes [20]

[1] Hospital Arnau de Vilanova, Valencia, Spain; Universidad Catolica de Valencia San Vicente Martir, Valencia, Spain; Medica Scientia Innovation Research (MEDSIR), Barcelona, Spain and Ridgewood, NJ, US [2] Instituto Valenciano de Oncología, Valencia, Spain [3] Hospital Universitario Virgen del Rocío, Sevilla, Spain [4] Hospital Clínico Universitario de Valencia; Biomedical Research Institute INCLIVA, Valencia, Spain [5] Institut Català d' Oncologia L'Hospitalet, Hospitalet de Llobregat, Barcelona, Spain [6] Hospital Reina Sofía, Cordoba, Spain [7] Hospital Universitario Virgen de la Victoria, Malaga, Spain [8] Institut Català d'Oncologia Badalona, Badalona, Spain [9] Hospital Arnau de Vilanova de Valencia, Valencia, Spain [10] Cancer Unit of Gipuzkoa, Osakidetza-Onkologikoa, Donostia, Spain [11] Hospital Arnau de Vilanova de Lleida, Lleida, Spain [12] Hospital Universitari Vall d'Hebrón, Barcelona; Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain [13] Hospital Universitario Miguel Servet, Zaragoza, Spain [14] International Breast Cancer Center (IBCC), Quiron Group, Barcelona, Spain; Medica Scientia Innovation Research (MEDSIR), Barcelona, Spain and Ridgewood, NJ, US [15] Hospital Universitario Ramón y Cajal, Madrid, Spain [16] Hospital del Mar, Barcelona, Spain [17] Complejo Hospitalario de Jaén, Jaén, Spain [18] Hospital Prof. Doutor Fernando Fonseca, Amadora, Portugal [19] Medica Scientia Innovation Research (MEDSIR), Barcelona, Spain and Ridgewood, NJ, US [20] International Breast Cancer Center (IBCC), Quiron Group, Barcelona; Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; Medica Scientia Innovation Research (MEDSIR), Barcelona, Spain and Ridgewood, NJ, US

BACKGROUND

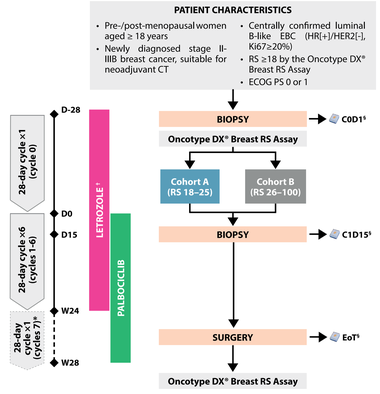
- Cyclin-dependent kinases 4 and 6 inhibitors (CDK4/6i) in combination with endocrine therapy frequently leads to a complete cell-cycle arrest (CCCA) in luminal early-stage breast cancer (EBC). However, the rates of pathological complete response (pCR) or Residual Cancer Burden (RCB) 0–I are modest [1-4].
- The 21-gene recurrence-score (RS) assay (Oncotype DX, Genomic Health) has proven to predict the risk of distant recurrence for patients (pts) with luminal EBC [5-6], providing information about the likely benefit from chemo-endocrine regimen [7-8].
- The effect of the addition of neoadjuvant CDK4/6i to endocrine therapy in terms of molecular downstaging assessed by a genomic signature such as the 21-gene RS assay remains undetermined.
- Switching from a high-risk to a low-risk RS group after exposure to neoadjuvant CDK4/6i plus endocrine therapy could provide useful information to identify pts who might not require adjuvant chemotherapy.

OBJECTIVE

- DxCARTES evaluated the biological effect and clinical activity of neoadjuvant administration of palbociclib in combination with letrozole in pts with stage II-IIIB luminal B-like EBC (HR-positive/HER2-negative, Ki67≥20%) with a RS ≥18.

STUDY DESIGN

Figure 1. DxCARTES Study Design (NCT03819010)



* Treatment with palbociclib plus letrozole was continued until surgery. If surgery had been delayed >14 days from the last palbociclib dose, patients received an additional cycle of palbociclib (cycle 7) immediately before surgery.
† Pre-registered patients can receive letrozole (with luteinizing hormone-releasing hormone analog if premenopausal), followed by adding palbociclib on cycle 1 day 1 (C1D1).
§ At baseline, day 15, and surgery, collection of tissue samples were mandatory to centrally assess changes of RS and Ki67 expression.

Abbreviations: C, cycle; D, day; CT, chemotherapy; EBC, early-stage breast cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; EoT, end of treatment; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; RS, recurrence score result; W, week.

METHODS

- This is a multicenter, open-label, two-arm, non-comparative, phase 2 trial (Figure 1).
- Based on the 21-gene RS determined at baseline, pts with a RS 18–25 were allocated to **cohort A** and those with a RS 26–100 to **cohort B**.
- Pts received six 28-day cycles of palbociclib (125 mg once daily on 3/1 schedule) in combination with letrozole (2.5 mg once daily continuously every 28-day cycle) ± Luteinizing Hormone-Releasing Hormone (LHRH) analog if premenopausal.

Co-Primary Endpoints

Cohort A and **Cohort B**

- To assess the rate of pts with baseline RS 18–25 in **cohort A** and RS 26–100 in **cohort B** who achieved a RS ≤25 by the 21-gene RS assay or a pCR in the breast and axilla (pCR_{BL}: ypT0/is, ypN0) or microscopic residual infiltration (if RS was not feasible at surgery) after neoadjuvant treatment.

Key Secondary Endpoints

Cohort A and **Cohort B**

- To assess at surgery the rate of pts in either cohort who had a pCR in the breast (pCR_B: ypT0/Tis), the change in RS rates, RCB [11] 0–1, preoperative endocrine prognostic index (PEPI) score of 0, conversion from mastectomy to breast-conserving surgery (BCS) and from N1 to N0, and the concordance rate between RS and CCCA (Ki67≤2.7%).
- To assess Ki67 expression rates at baseline, C1D15, and surgery.
- To assess the best response and overall response as per RECIST 1.1.
- To evaluate safety and tolerability as per NCI-CTCAE v.5.0.

Statistics

- For the co-primary endpoints analysis, pts who received study drug and had at least the baseline RS measurement were considered (33 in **cohort A** and 34 in **cohort B**).
- For secondary endpoints analysis, pts who received study drug and had both baseline and surgery RS measurements were considered (32 in **cohort A** and 30 in **cohort B**).
- The analyses were designed to attain an 80% power, with a 10% drop out rate assumption, at a nominal 1-sided α level of 2.5%.

Cohort A

- Simon's optimal 2-stage design based on excluding a biological stabilization rate (RS ≤25 or pCR_{BL}) ≤72% while targeting a biological stabilization rate to ≥ 93%.
- Final analysis: 28 evaluable pts among 33 pts recruited (positive finding with ≥ 25 pts with biological stabilization).

Cohort B

- Simon's minimax two-stage design based on excluding a biological response rate (RS ≤25 or pCR_{BL}) ≤13% while targeting a biological response rate to ≥ 35%.
- Final analysis: 28 evaluable pts among 33 pts recruited (positive finding with ≥ 8 pts with biological response).

RESULTS

1. Recruitment And Patient Disposition

- Between May 8, 2019, to December 30, 2019, 67 pts were allocated in **cohort A** (n=33) and **cohort B** (n=34) across 17 hospitals in Spain (Table 1).
- Data cutoff date: October 29, 2020.
- Time from enrollment to data cutoff, median (IQR):
  - 5.6 months (range: 2.2 – 6.9) in **cohort A**;
  - 5.5 months (range: 1.9–6.7) in **cohort B**.

Table 1. Baseline Characteristics In ITT Population

Characteristic	Cohort A (n=33)	Cohort B (n=34)
Age, median (range) years	57 (40.0–80.0)	57.5 (40.0–79.0)
Tumor size		
T1	0 (0)	1 (2.9)
T2	29 (87.9)	25 (73.5)
T3	3 (9.1)	8 (23.5)
T4	1 (3.0)	0 (0)
Lymph node status		
N0	16 (58.5)	18 (52.9)
N1	17 (51.5)	13 (38.2)
N2	0 (0)	3 (8.8)
Clinical stage		
IIA	14 (42.4)	16 (47.1)
IIB	17 (51.5)	12 (35.3)
IIIA	1 (3.0)	6 (17.6)
IIIB	1 (3.0)	0 (0)
Tumor grade		
I (well differentiated)	4 (12.1)	2 (5.9)
II (moderately differentiated)	15 (45.5)	17 (50.0)
III (poorly differentiated)	8 (24.2)	7 (20.6)
Unknown	6 (18.2)	8 (23.5)
Menopausal status		
Pre-Menopausal	11 (33.3)	11 (32.3)
Post-Menopausal	22 (66.7)	23 (67.7)
ECOG performance status		
0	30 (90.9)	31 (91.2)
1	3 (9.1)	3 (8.8)
ER expression		
Negative (<1%)	-	-
Low-positive (1–9%)	1 (3.0)	1 (2.9)
Positive (≥10%)	32 (97.0)	33 (97.1)
PR expression		
Negative (<1%)	3 (9.1)	9 (26.5)
Low-positive (1–9%)	4 (12.1)	1 (2.9)
Positive (≥10%)	26 (78.8)	24 (70.6)
Proportion of cells with Ki67 in a sample, median (range)	25.0 (20.0–50.0)	30.0 (20.0–75.0)
Time from diagnosis in days, median (range)	43.0 (25.0–141.0)	42.0 (30.0–91.0)
Surgical intent at baseline		
Breast-conserving surgery	28 (84.8)	27 (79.4)
Mastectomy	5 (15.2)	7 (20.6)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; PR, progesterone receptor

2. Co-Primary Endpoints: Biological Stabilization After Treatment

- In **cohort A**, 22 of 33 pts (66.7%) had RS ≤25 after treatment, failing to reach the primary endpoint ($P = 0.779$).
- In **cohort B**, 18 of 34 pts (52.9%) had RS ≤25 or experienced a pCR after treatment, meeting the primary endpoint (**$P < 0.001$**).

Table 2. Secondary Efficacy Endpoints

Characteristic	Cohort A (n=33)	Cohort B (n=34)
Recurrence score rates at surgery		
Recurrence score 0–17	6 (18.8)	5 (16.7)
Recurrence score 18–25	16 (50.0)	13 (43.3)
Recurrence score 26–100	10 (31.2)	12 (40.0)
pCR_{BL} (ypT0/is, ypN0)	0 (0)	1 (3.3)
pCR_B (ypT0/is)	3 (9.4)	2 (6.7)
RCB 0–I	1 (3.1)	2 (6.7)
PEPI score 0	3 (9.4)	8 (26.7)
Conversion from mastectomy to BCS	2 (6.3)	3 (10.0)
Conversion from N1 to N0 lymph node status	n=17 1 (5.9)	n=16 3 (8.8)
Ki67 expression at C1D15	n=25	n=24
0–2.7%	21 (84.0)	16 (66.7)
2.8–9%	2 (8.0)	7 (29.2)
10–19%	0 (0)	0 (0)
≥20%	2 (8.0)	1 (4.2)
Not evaluated	8	10

Complete cell cycle arrest (CCCA: central Ki67 ≤2.7%).

Figure 2. Correlation Of RS With CCCA At Surgery

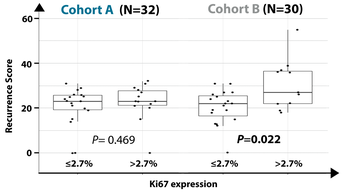
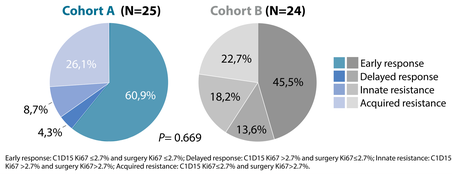


Figure 3. Treatment Response By Ki67 Expression



Early response: C1D15 Ki67 ≤2.7% and surgery Ki67 ≤2.7%; Delayed response: C1D15 Ki67 >2.7% and surgery Ki67≤2.7%; Innate resistance: C1D15 Ki67 >2.7% and surgery Ki67>2.7%; Acquired resistance: C1D15 Ki67≤2.7% and surgery Ki67>2.7%.

Table 3. Tumor Response As Per RECIST 1.1

Best response *, n (%)	Cohort A (n=33)	Cohort B (n=34)
Complete Response	2 (6.3)	4 (12.5)
Partial response	23 (71.9)	17 (53.1)
Stable disease	6 (18.8)	8 (25.1)
Progressive disease	0 (0)	2 (6.3)
Not evaluated	2 (6.1)	3 (8.8)
Overall Response Rate	25 (78.1)	21 (64.0)

* Calculated over a total of 67 patients who underwent breast ultrasound both at baseline and immediately before surgery or patient discontinuation.

Table 4. Drug-Related TEAEs In ≥10% Of Patients

AEs, n (%)	Cohort A (n=33)		Cohort B (n=34)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
Any	30 (90.9)	20 (60.6)	32 (94.1)	14 (41.2)
Hematologic				
Neutropenia	23 (69.7)	18 (54.5)	20 (58.8)	13 (38.2)
Leukopenia	7 (21.2)	1 (3.0)	3 (8.8)	0 (0)
Thrombocytopenia	4 (12.1)	0 (0)	1 (2.9)	0 (0)
Non-Hematologic				
Asthenia	11 (33.3)	0 (0)	8 (23.5)	0 (0)
Stomatitis	8 (24.2)	0 (0)	7 (20.6)	0 (0)
Hot flush	7 (21.2)	0 (0)	2 (5.9)	0 (0)
Fatigue	5 (15.2)	0 (0)	2 (5.9)	0 (0)

- No patient suffered any drug-related serious adverse event.
- One patient in **cohort A** was discontinued due to an unrelated myocardial infarction.
- No deaths due to AE were reported.

CONCLUSIONS

- Our results suggest that a significant proportion of HR[+]/HER2[-] EBC pts with high RS at baseline achieve a molecular downstaging after neoadjuvant treatment with palbociclib plus letrozole, despite the unknown prognostic value of the molecular downstaging.
- Further investigation is needed in larger cohorts to validate these findings and to determine if this strategy could avoid the use of chemotherapy in this population.

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