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Neoadjuvant letrozole and palbociclib in stage II-IIIB HR[+]/HER2[-] breast cancer with Oncotype DX Recurrence Score® (RS) 18-25 or 26-100. Analysis of RS changes at surgery (DxCARTES trial) Short Title: RS after NAT letrozole+palbociclib

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Background

- The combination of a CDK4/6 inhibitor (palbociclib, abemaciclib, or ribociclib) with an aromatase inhibitor (AI) significantly reduces Ki67 compared to single-agent AI in the neoadjuvant setting. However, the rates of pathological complete response (pCR) or Residual Cancer Burden (RCB) 0-I remain modest [1-3].
- Despite this inadequate pathological downstaging, to date, there is no data about the efficacy of this treatment in terms of molecular downstaging detected by a more refined genomic signature than Ki67, such as the Oncotype DX Breast Recurrence Score® (RS) test.
- The aim of this trial is to validate the ability of neoadjuvant palbociclib plus letrozole to modify two initial intermediate or high RS tumor cohorts of patients with hormone receptor (HR)-positive, Human Epidermal Growth Factor Receptor 2 (HER2)-negative, early, large operable, and locally advanced breast cancer (BC), who have not previously received any systemic therapy.

Key selection criteria

A) Inclusion Criteria:

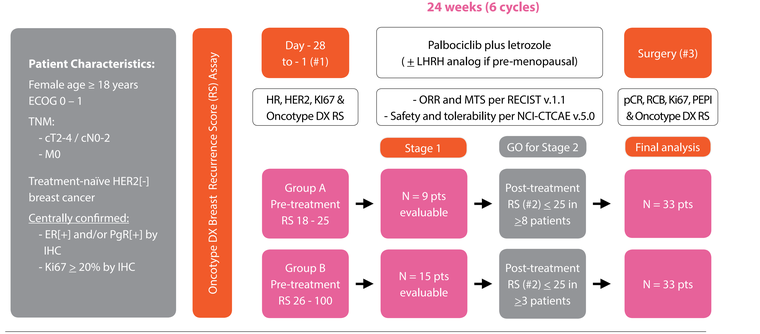
1	Female patients over 18 years of age.
2	Measurable disease (tumor size > 2.0 cm) by mammogram and/or breast ultrasound (according to Response Evaluation Criteria in Solid Tumors [RECIST] v.1.1).
3	Node-negative or limited node involvement (N0-2, according to TNM staging system) assessed by ultrasound ± fine needle aspiration.
4	Centrally confirmed HR[+] BC.
5	HER2[-] BC by local assessment using an in situ hybridization test or negative immunohistochemical (IHC) status of 0, 1+ or 2+. If IHC is 2+, a negative in situ hybridization test is required.
6	Ki67 levels ≥ 20% confirmed by IHC testing in a central laboratory.
7	Oncotype DX Breast Recurrence Score® (RS) ≥ 18.
8	Eastern Cooperative Oncology Group (ECOG) performance status of 0-1.
9	Adequate organ function.

B) Exclusion Criteria:

1	Evidence of metastatic disease by routine clinical assessment.
2	Inflammatory BC.
3	Bilateral BC.
4	Multifocal or multicentric BC.
5	Prior chemotherapy, endocrine therapy, or radiotherapy for current disease.
6	Other malignancies within the past five years except adequately treated basal cell or squamous cell skin cancer or carcinoma in situ of the cervix.

Trial design

- This is an international, multicenter, open-label, non-comparative, phase II trial.
- Patients will receive treatment with palbociclib (125 mg daily, 3/1 schedule) in combination with letrozole (2.5 mg daily, every 28-day cycle), ± Luteinizing Hormone-Releasing Hormone (LHRH) analogs if pre-menopausal status, for 24 weeks.
- Definitive breast surgery will be performed within 7 days after completion of 6 treatment cycles.



#1 Pre-registered patients can receive up to 4 weeks of letrozole before inclusion.
#2 Post-treatment RS ≤ 25 or a pCR/microscopic residual infiltration where the post-treatment RS result is not feasible.
#3 If surgery is delayed, patients must receive additional palbociclib plus letrozole treatment until immediately before surgery.
cN: Node classification; cT: Tumor classification; ER: Estrogen receptor; HER2: Human Epidermal Growth Factor Receptor 2; HR: Hormone Receptor; IHC: Immunohistochemistry; LHRH: Luteinizing Hormone-Releasing Hormone; M: Metastasis classification; MTS: Maximum Tumor Shrinkage; NCI-CTCAE: National Cancer Institute–Common Terminology Criteria for Adverse Events; ORR: Overall response rate; pCR: Pathological complete response; PEPI: Preoperative Endocrine Prognostic Index; PgR: Progesterone receptor; RECIST: Response Evaluation Criteria in Solid Tumors; RS: Oncotype DX Breast Recurrence Score® Assay; TNM: Tumor-node-metastasis classification for breast cancer; RCB: Residual Cancer Burden

Primary objective

- To explore the ability of palbociclib in combination with letrozole to induce global molecular changes, measured by either the post-treatment RS result at surgery, or pCR in patients with aggressive luminal tumors (pre-treatment RS result 18-25 or 26-100, and Ki67 ≥ 20%).

1st Co-primary endpoint:

- The percentage of patients in cohort A (pre-treatment RS 18-25) that experience a biological stabilization*.

2nd Co-primary endpoint:

- The percentage of patients in cohort B (pre-treatment RS 26-100) that experience a biological response*.

** The biological stabilization or response is defined as achievement of a post-treatment RS ≤ 25 or a pCR/microscopic residual infiltration where the post-treatment RS result is not feasible.*

Sample size

- The total accrual will be 66 patients, with 33 patients included in each cohort.
- We expect to screen a total of 165 newly-diagnosed HR[+]/HER2[-] with Ki67 ≥ 20%, early, large operable, and locally advanced BC patients.

Cohort A (RS 18–25):

- Simon's optimal two-stage design based on excluding a biological stabilization rate ≤ 72% while targeting a biological stabilization rate to ≥ 93%.
- 1st stage: 9 evaluable patients among 12 patients recruited (futility stop ≤ 7 patients with biological stabilization).
- Final analysis: 28 evaluable patients among 33 patients recruited (positive finding with ≥ 25 patients with biological stabilization).

Cohort B (RS 26–100):

- Simon's minimax two-stage design based on excluding a biological response rate ≤ 13% while targeting a biological response rate to ≥ 35%.
- 1st stage: 15 evaluable patients among 18 patients recruited (futility stop ≤ 2 patients with biological response).
- Final analysis: 28 evaluable patients among 33 patients recruited (positive finding with ≥ 8 patients with biological response).
- The study is designed to attain and 80% power at nominal level of one-sided alpha of 0.025 in each cohort.

Method of primary analysis

- We will report % of patients with biological stabilization or response.
- The P-value and 95% confidence intervals will be based on uniformly minimum variance unbiased estimator (UMVUE).

Secondary objectives

Molecular endpoints:

- RS reduction in patients included in cohort A.
- RS increase in patients included in cohort A.
- RCB.
- 2-week Ki67 index changes.
- pCR.
- Perioperative endocrine prognostic index (PEPI) score.
- Concordance rate among post-treatment RS result and RCB, Ki67, pCR, and PEPI score.

Efficacy-related endpoints:

- Overall response rate (RECIST v.1.1).
- Maximum Tumor Shrinkage (RECIST v.1.1).

Safety-related endpoints:

- Adverse events in accordance with Common Terminology Criteria for Adverse Events v. 5.0.

References

1. C. X. Ma et al. "NeoPalAna: Neoadjuvant Palbociclib, a Cyclin-Dependent Kinase 4/6 Inhibitor, and Anastrozole for Clinical Stage 2 or 3 Estrogen Receptor-Positive Breast Cancer." Clin Cancer Res. 2017;23(15):4055-4065. Doi: 10.1158/1078-0432.CCR-16-3206.
2. M Martin, et al. "Final results of NeoMONARCH: A phase 2 neoadjuvant study of abemaciclib in postmenopausal women with hormone receptor positive (HR+), HER2 negative breast cancer (BC)." Cancer Research 2018; 78(4):PD5-01. Doi:https://doi.org/10.1158/1538-7445.SABCS17-PD5-01.
3. Chow LWC, et al. "Neoadjuvant palbociclib on ER+ breast cancer (N007): clinical response and EndoPredict's value." Endocr Relat Cancer. 2018; 25(2): 123–130. Doi: 10.1530/ERC-17-0396.

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Trial Registration: NCT03819010.
Date: March 7th, 2019.
First Patient First Visit:
Expected on April 2019.