Impact of locoregional treatment after 6 months of Palbociclib + Letrozole combination therapy in *de novo* ER+, HER2- metastatic breast cancer patients: first results of the prospective PALATINE trial

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Abstract

We present the first results of a prospective multicentric, single arm, phase II trial aiming to **evaluate the overall survival (OS) rate at 24 months in ER+/HER2- *de novo* mBC patients.**

Introduction

***De novo* metastatic breast cancer** (mBC) accounts for approximately **30% of ER+/HER2- mBC**. Treatment relies on systemic therapy. Retrospective and prospective trials have attempted to demonstrate the benefit of locoregional treatment on overall survival (OS) with mixed results. However, all these trials were before the CDK4/6 inhibitors era.

The primary objective of the present trial was to **evaluate the overall survival (OS) rate at 24 months in ER+/HER2- *de novo* mBC patients receiving palbociclib plus letrozole combination with a planned locoregional therapy after 6 months of systemic treatment.**

Methods and Materials

We conducted a **prospective multicentric, single arm, phase II trial**, including women from 23 centers with *de novo* ER+/HER2- mBC. Patients with advanced, symptomatic, visceral spread, at risk of short-term, life-threatening complications and visceral crisis, were excluded.

All patients received **palbociclib + letrozole for 24-26 weeks,** followed by a locoregional treatment of the investigator's choice: **surgery and/or radiation therapy** (RT). Palbociclib and letrozole were continued until progression.

Assuming that a 24-month overall survival (OS) rate of 88% or lower is not clinically meaningful, and aiming for 93% **power to detect a 24-month OS rate of 94% or higher**, a total of 191 patients are required (one-sided alpha of 7%).

Table 1. Characteristics of patients with unilateral breast cancer

	UNILATERAL BC, n(%) N=183
CLINICAL SIZE (mm)	
- Mean (SD)	39.8 (22.6)
- NA	13
T (TNM)	
- T1–T2	80 (53.0%)
- T3–T4	71 (47.0%)
N (TNM)	
- N0	31 (22.5%)
- N1	79 (57.2%)
- N2	19 (13.8%)
- N3	9 (6.5%)
- NA	45
HISTOLOGICAL TYPE	
- Ductal	124 (68.1%)
- Lobular	34 (18.7%)
- Other	21 (11.5%)
- Mixed (ductal + lobular)	3 (1.6%)
- NA	1
ELSTON-ELLIS GRADE	
- Grade I	17 (9.6%)
- Grade II	132 (74.2%)
- Grade III	29 (16.3%)
- NA	5

Table 2. Locoregional treatment

	Surgery N=127	No surgery N= 71	NA
Radiotherapy	**112 (56.6%)**	26 (13.1%)	0
No radiotherapy	15 (7.6%)	45 (22.7%)	0
NA	0	0	1

Results

From 2019 to 2022, 209 patients were screened, 199 were evaluable and **191 patients were analyzed in ITT**.

Median age was **56 years** (range 26-86) and 59% of patients (59%) were post-menopausal (N=115). For the 183 patients with unilateral BC, the **median tumoral size was 37.5 mm** (range <1-120), **85.8% had local lymph node involvement** (N=91) and tumors were mostly grade II (74.2%, N=132) or III (16.3%, N=29) with a **mean Ki67 at 27%**. 95.5% of patients had 3 or fewer metastasis sites (N=190) with 18.6% having bone-only metastases (N=37).

All patients received at least one cycle of **palbociclib and letrozole with a median duration of 22 months** (IQR 10.6-31.8). Then, **77.3% of patients received a locoregional treatment**. **56.6% had surgery and RT** (N=112), 7.6% had surgery only (N=15) and13.1% had RT only (N=26). 22.7% didn't receive any locoregional treatment (N=45).

After a median follow-up of 24.6 months (range 2-48.9), 42 patients died. **The 2-year OS rate estimated by Kaplan-Meier in the ITT population was 85.2%** (CI95%: 80.2 - 90.5), below the lower limit of 91.1% calculated by the Fleming method.

We observed 93 recurrence events with a **2-year progression free survival at 58.1%** (IC95%: 51.4 - 65.5), including 8.5% of patients with a local recurrence (N=17).

186 (93.5%) patients presented at least one adverse event (AE) linked to either systemic or locoregional treatment. Common AE of palbociclib-letrozole were neutropenia (64.3%) including 41.7% grade (gr) 3 and 5.5% gr 4, fatigue (61.3%) mainly gr 1 (46.7%), gastrointestinal disorders (51.8%) of which 36.2% gr 1, 13.6% gr 2 and 2% gr 3, and hot flushes (32.2%) mainly gr 1(22.6%). AEs reported with RT were skin disorders (27.6%) of which 17.6% gr 1 and 7% gr 2, and 8% gr 1 fatigue. Surgery induced 7.5% gr 1, 4 % gr 2 and 0.5% gr 3 AEs, notably 3% gr 1 breast pain and 2.5% gr 1 lymphocele.

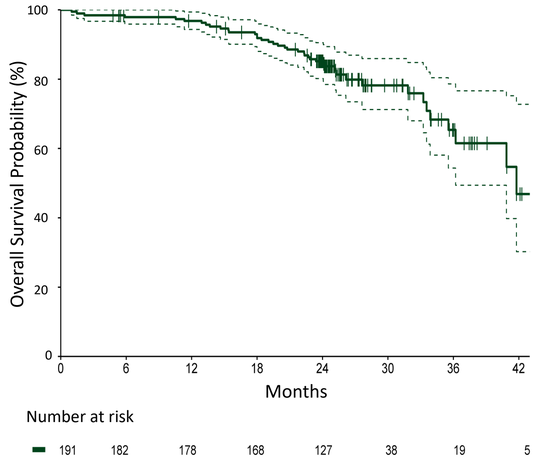


Figure 1. Overall survival

Conclusions

In patients with *de novo* ER-positive/HER2-negative metastatic breast cancer, **locoregional treatment after 6 months of palbociclib + letrozole is feasible, well tolerated, and provides excellent local control, but was not associated with the expected 24-month OS.** These results suggest that the decision to perform locoregional therapy should be **individualized**, considering metastatic burden, toxicity profile, patient preferences and risk of local progression that could threaten patients' QoL.

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