REAL-WORLD TREATMENT PATTERNS AND OUTCOMES OF SELECTIVE CYCLIN-DEPENDENT KINASE (CDK) 4/6 INHIBITORS UTILIZATION IN METASTATIC BREAST CANCER – REVEAL STUDY

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Background and importance

Active involvement of hospital pharmacists in real-world effectiveness studies is paramount to generate evidence about the value of innovative medicines in clinical practice. The REVEAL study was designed and implemented by a cooperative research group of hospital pharmacist to assess the therapeutic value of current standard of care with CDKi4/6 in HER2-negative, hormone receptor-positive metastatic breast cancer (MBC:HR+;HER2(-)).

Aim and objectives

- **To characterize treatment patterns of CDK4/6 inhibitors palbociclib and ribociclib use in women with MBC.**
- **To quantify dose adjustments until six months of CDKi4/6 treatment.**
- **To estimate persistence on treatment with ribociclib at 12 and 24 months.**

Materials and methods

Retrospective observational cohort study, including adult women with MBC:HR+;HER2(-) who used CDKi4/6 (ribociclib or palbociclib) in addition to hormone therapy. This study was characterized as a drug utilization study (DUS), based in data records from 7 participating Hospital Pharmaceutical Services.

This study comprises **two stages**:

• **Identification**: patients who have started therapy with CDKi 4/6 (ribociclib and palbociclib) between 1 March and 31 December 2019.

• **Follow-up**: until June 2020 to quantify the occurrence and extent of dose modification and until 24 months to assess persistence on treatment with ribociclib (last observation 31st of December 2021).

The **inclusion criteria** were as follows:

• Female patients;

• Aged ≥18 years at CDKi 4/6 initiation;

• Patients with diagnosis of MBC HR-positive and HER2-negative;

• Patients with the first claim of palbociclib or ribociclib during the identification period.

Patients with electronic claims of both CDKi 4/6 during the study period were considered eligible for study inclusion. Patients with missing information regarding date of birth and date or quantity of drug dispensed in any claim were excluded.

Menopausal status, treatment line, dose modifications and persistence of treatment were defined according to the following assumptions:

• Menopausal status: if the patient has been administered goserelin, within six months before or after the CDKi initiation, she will be considered as an induced menopausal woman. For those without goserelin claim, if less than 50 years, it was considered induced menopausal and if equal or above 50 years, it was considered natural menopause.

• Treatment line: patients with concomitant treatment with fulvestrant and any CDKi during the study period were assumed as being in the second line treatment for advanced disease. To further confirm this information, data from drugs dispensed, namely aromatase inhibitors or tamoxifen, on the previous 12 months were also collected. If a patient had fulvestrant and CDKi, without any previous aromatase inhibitors or tamoxifen, this treatment was considered as a first line.

• Dose modifications: any change of dose or amount of CDKi dispensed.

• Persistence of treatment: patients were considered persistent if the period between claims was less than 30 days.

Descriptive statistics (mean, standard deviation, minimum and maximum) were used to summarized the demographic and clinical of sample characteristics. Comparisons between CDKi were preformed using Fisher's exact test. Probability of persistence (survival) with ribociclib, was estimated using the Kaplan-Meier estimator. A significance level of 5% was adopted. Statistical analyses were performed using R software version R 4.1.1®.

Study protocol was approved by hospitals' Ethics Committees.

RESULTS

We included 121 women from 7 public hospitals: palbociclib (n=86;71.1%); ribociclib (n=35;28.9%). The average age (min;max) was 58 (27;92) years (Table 1).

Most patients started CDKi4/6 treatment in postmenopause (n=85; 70.2%) and as second-line therapy (n=87; 71.9%). Combination with hormonal therapy was: Aromatase inhibitors 97% in ribociclib and 71% in Palbociclib patients (p-value=0.003); fulvestrant in 6.1% ribociclib and 33.9% palbociclib patients (p-value=0.003) (see Table 2). The majority (76%) of patients had no dose adjustment in the first six months. There were no significant differences in the proportion of patients with dose modifications according to CDK4/6 inhibitor, patient's age, type of hormonotherapy or therapy line.

Table 1 Demographic and clinical characteristics.

	Total (n=121)	Palbociclib (n=86)	Ribociclib (n=35)
Age, Mean ± SD	58 ± 13	59 ± 13	58 ± 11
[Min, Median, Max]	[27, 59, 92]	[27, 59, 92]	[40, 59, 77]
Menopausal status, n (%)			
Premenopausal	36 (29.8%)	26 (30.2%)	10 (28.6%)
Postmenopausal	85 (70.2%)	60 (69.8%)	25 (71.4%)
CDKi4/6 therapy			
First line	34 (28.1%)	15 (17.4%)	19 (54.3%)
Second line	87 (71.9%)	71 (82.6%)	16 (45.7%)

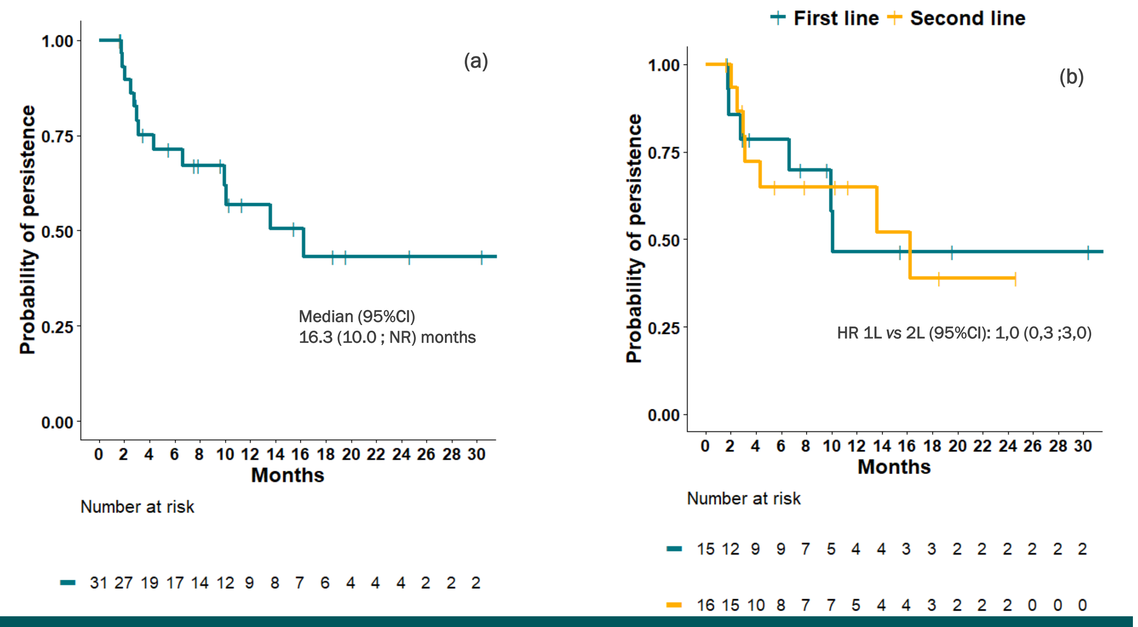
Table 2 CDKi4/6 treatment and concomitant endocrine therapy.

	Total	Palbociclib	Ribociclib	p-value*
	N=121	N = 86	N = 35	
Without concomitant therapies, n (%)	26 (21.5%)	24 (27.9%)	2 (5.7%)	0.007
Concomitant therapies, n (%)				
Goserelin	5 (5.3%)	2 (3.2%)	3 (9.1%)	0.34
Fulvestrant	23 (24.2%)	21 (33.9)	2 (6.1%)	0.003
Tamoxifen	3 (3.2%)	2 (3.2%)	1 (3.0%)	>0.99
Aromatase Inhibitors	76 (80.0%)	44 (71.0%)	32 (97.0%)	0.003

*Fisher's exact test or Pearson's chi-squared test

There were no significant differences in the proportion of patients with dose modifications according to CDK4/6 inhibitor, patient's age, type of hormonotherapy or therapy line. The median persistence on treatment with ribociclib was 16.3 months (95%CI=[10;NA]). Persistence [95%CI] on treatment with ribociclib at 12 months was 57% [40%;81%] and at 24 months 43% [26%;73%] (Figure 1 a). No significant differences were observed in the probability of ribociclib persistence by line of treatment (Figure 1 b).

Figure 1 Persistence to ribociclib: a) overall; b) by line of treatment.



Conclusion and relevance

The REVEAL study confirmed the effectiveness of CDKi4/6 in real-world settings, including dose adjustments and persistence on treatment. Leadership in real-world effectiveness studies is paramount to elevate the role of pharmacists in establishing the therapeutic value of innovative medicines.

Conflict of Interest: This project was developed within the framework of a clinical research collaboration protocol established between Novartis Farma, Produtos Farmacêuticos S.A., Exigo Consultores and a group of Portuguese hospitals