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Observational real world data with palbociclib associated to hormone therapy for advanced breast carcinoma

Estudio observacional de práctica habitual con palbociclib y hormonoterapia para carcinoma de mama avanzado

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Abstract

Objective: Cyclin-dependent kinase 4/6 inhibitors have a synergistic effect in combination with endocrine therapy. This combination is used as first and subsequent-line treatment for advanced luminal breast carcinoma because it increases progression-free survival. We analysed clinical course and toxicity in patients treated with palbociclib in our hospital and determined potential associations between these variables and clinicopathological variables.

Method: Observational retrospective study including patients with advanced or metastatic breast cancer treated with palbociclib plus endocrine therapy at the Hospital Universitario de Cabueñes between 2017 and 2020. We analysed clinicopathological variables, toxicity, and survival.

Results: In total, 72 women and 1 man (median age: 63 years) received palbociclib plus an aromatase inhibitor or fulvestrant. When used as first-line treatment, progression-free survival was 22 months, and as second and subsequent-line treatment, progression-free survival was 13 months. Adverse effects (mainly haematological) were experienced by nearly all

KEYWORDS

Breast cancer; Cyclin-dependent kinase inhibitor proteins; Palbociclib; Aromatase inhibitors; Fulvestrant; Drug-related side effects and adverse reactions; Progression-free survival.

Resumen

Objetivo: Los inhibidores de quinasas dependientes de ciclina CDK4 y CDK6 poseen efecto sinérgico al asociarse con hormonoterapia. Su uso está extendido en primera y sucesivas líneas de carcinoma de mama avanzado tipo luminal por mejorar la supervivencia libre de progresión. Los objetivos de nuestro estudio se basaron en analizar la evolución clínica y la toxicidad presentada en las pacientes tratadas en nuestro centro con palbociclib, así como relacionar la evolución con las diferentes variables clínico-patológicas.

Método: El estudio, de tipo observacional y retrospectivo, recogió datos de pacientes con cáncer de mama avanzado o metastásico tratados con hormonoterapia y palbociclib en el Hospital Universitario de Cabueñes entre los años 2017 y 2020. Se analizaron diferentes variables clínico-patológicas, así como información sobre toxicidad y supervivencia.

Resultados: Un total de 72 mujeres y 1 varón con una mediana de edad de 63 años recibieron palbociclib asociado a inhibidor de aromatasa o fulvestrant. En primera línea la supervivencia libre de progresión fue de 22 meses, y en segunda o sucesivas líneas de 13 meses. El 95,9% de

PALABRAS CLAVE

Neoplasias de mama; Proteínas inhibidoras de las quinasas dependientes de la ciclina; Palbociclib; Inhibidores de aromatasa; Fulvestrant; Efectos colaterales y reacciones adversas relacionados con medicamentos; Supervivencia sin progresión.

patients (95.9%). Treatment was not discontinued because of toxicity in any patient, although delays and dose adjustments were common (61.7% and 42.7%, respectively). Performance status alone had a significant impact on progression-free survival (22 months in patients with ECOG 0 vs 12 months in patients with ECOG ≥ 1; *P* = 0.021).

Conclusions: Disease stage, age, and performance status do not limit the use of treatment with palbociclib, nor its combination with aromatase inhibitors or fulvestrant for first or subsequent-line treatment. Toxicity is easily managed. Real-world results are equivalent to those published to date.

las pacientes presentaron algún tipo de efecto adverso, principalmente hematológico. No se produjo ningún abandono por toxicidad, aunque los retrasos y los ajustes de dosis fueron frecuentes (61,7% y 42,7%, respectivamente). Solo la situación funcional al inicio del tratamiento influyó de manera significativa en la supervivencia libre de progresión (22 meses en ECOG 0 *versus* 12 meses en ECOG ≥ 1; p = 0,021).

Conclusiones: La extensión de la enfermedad, edad o *status* menopáusico no impiden el tratamiento con palbociclib, ya se administre con inhibidores de aromatasa o fulvestrant y en una u otra línea metastásica. La toxicidad del fármaco es manejable, y los resultados de vida real obtenidos son superponibles a los de los ensayos publicados hasta la actualidad.

Introduction

For many years, advanced breast cancer with hormone receptor (HR) expression has been treated by blocking the oestrogen receptor signalling pathway[1]. Recently, new endocrine therapies have been developed that offer improved benefits by increasing overall survival[2]. However, some patients are resistant to these drugs, leading to the search for alternatives or drugs that enhance their antihormonal activity. Cyclin-dependent kinases (CDKs) are a family of serine-threonine kinases that have a role in regulating the cell cycle. The interaction of cyclin D with CDK4 and CDK6 facilitates the hyperphosphorylation of the retinoblastoma (Rb) protein, leading to the transition from the G1 phase (checkpoint) to the S phase of the cell cycle. Alterations in this cycle lead to the loss of regulation of these checkpoints and trigger the development of neoplasms or resistance mechanisms. A feature of luminal breast cancer is the activation of the CDK4/CDK6/E2F axis. Hormone therapy partly inhibits CDK4 and CDK6 activity, and thus the reactivation of these kinases may be involved in endocrine resistance[3,4].

Palbociclib is a small molecule and is a selective inhibitor of CDK4 and CDK6[5]. Preclinical studies have shown its ability to prevent the growth of breast cancer cells expressing oestrogen receptors, enhance the activity of anti-oestrogens, and reverse endocrine resistance[3]. These results have led to multiple clinical trials within the Palbociclib: Ongoing Trials in the Management of Breast Cancer (PALOMA) program, in which palbociclib plus different endocrine therapies is being evaluated for the treatment of metastatic breast cancer and at different times over the course of the disease. To date, the most relevant trials are PALOMA-1 (phase 2 with letrozole ± palbociclib as first-line monotherapy)[6], PALOMA-2 (phase 3, designed to confirm the results of the PALOMA-1 study)[7], and PALOMA-3 (phase 3 with fulvestrant ± palbociclib in advanced breast cancer, regardless of menopausal status and line of treatment)[8,9]. Based on evidence from these trials, the US Food and Drug Administration and the European Medicines Agency have authorised its use as first-line treatment plus an aromatase inhibitor and as second-line treatment plus fulvestrant for HR-positive/human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer.

Palbociclib is metabolized in the liver and eliminated as metabolites in urine and faeces. Regarding its safety profile, the most frequent adverse reactions (≥ 20%) of any grade reported in clinical trials are neutropenia, infections, leukopenia, tiredness, nausea, stomatitis, anaemia, diarrhoea, alopecia, and thrombocytopenia. The most frequent ≥ grade 3 adverse reactions (≥ 2%) are neutropenia, leukopenia, infections, anaemia, elevated aspartate aminotransferase, tiredness, and elevated alanine aminotransferase. In the trials, adverse reactions led to dose reductions or modifications in 38.4% of treated patients and permanent discontinuation in 5.2%, regardless of the combination[3,7,9].

Two other CDK4/6 inhibitors (ribociclib and abemaciclib) plus hormone therapy (HT) have been authorised as first or successive-treatment lines for luminal breast cancer. Previous metaanalyses have confirmed their benefit without demonstrating superiority of one over the other[10-12]. Adverse effects are more common with CDK4/6 inhibitors plus HR than with monotherapy, and grade 3-4 toxicity increases from 20% to 70%. The three drugs have qualitatively similar adverse effects, but they differ in their frequency and nature. Neutropenia can occur with any of the three, but is a dose-limiting effect of palbociclib and ribociclib. Tiredness is more frequent with palbociclib and abemaciclib, although digestive toxicity is more intense with abemaciclib. Cardiac and liver monitoring are required with ribociclib as it prolongs the QTc interval and increases liver enzymes. Abemaciclib is the only drug authorised as monotherapy after HT and prior to chemotherapy. It penetrates the blood-brain barrier and thus can be considered the drug of choice when there is central nervous system involvement[13]. Palbociclib must be taken with meals and abemaciclib does not have on/off periods, which may affect patient preferences. Cost-effectiveness studies vary between countries, as do the economic policies of the autonomous communities in Spain, both of which lead to differences in access to oncological drugs at both the national and international level[14].

This study had the following objectives: to analyse the clinical course of patients receiving HT plus palbociclib in our hospital, to assess toxicity secondary to the combined treatment and its management in each patient, and to analyse potential correlations between clinical course and the clinicopathological characteristics of the patients.

Methods

Data were retrospectively collected from patients with advanced or metastatic breast cancer who started treatment with PHT plus palbociclib at the Hospital Universitario de Cabueñes between January 1, 2017 and December 31, 2019. Clinical follow-up ended on September 1, 2020.

Inclusion criteria for the clinical study were as follows:

- A clinical history was available.
- The presence of a tumour with HR expression and without HER2 expression.

Exclusion criteria were as follows:

- Failure to complete at least one treatment cycle.
- Clinical follow-up not possible.

The study had an observational design with no interventions by the investigator. It was limited to measuring the following clinicopathological variables: sex, age, Eastern Cooperative Oncology Group (ECOG) performance status, menopausal status, number of previous hormonal lines including adjuvant, previous chemotherapy (including adjuvant), type of HT received, previous sensitivity to HT, HT plus palbociclib, disease stage, toxicity, duration of treatment with palbociclib, follow-up, and current disease status. Clinical course was assessed by progression-free survival (PFS), which was defined as the time from starting palbociclib treatment until disease progression according to *Response Evaluation Criteria in Solid Tumors* (RECIST). The type and degree of toxicity were classified according to *Common Terminology Criteria for Adverse Events* (CTCAE 5.0). Data were also collected on modifications to the palbociclib dosing regimen (dose reductions or delays between cycles) as well as treatment discontinuation due to toxicity.

Unless contraindicated by medical criteria, patients were started on 125 mg/24 h palbociclib for 21 treatment days followed by 7 rest days, repeating the cycle thereafter. The Medical Oncology and Onco-Haematology Pharmacy departments emphasized the importance of taking the treatment with food and always at the same time, and also provided oral and written information on missed doses, possible drug interactions, and the management of adverse reactions. Individualized doses were adjusted according to the safety and tolerability data described in the Summary of Product Characteristics. Treatment with palbociclib was continued until the

appearance of unacceptable toxicity or disease progression. Pre/perimenopausal women started treatment with luteinizing hormone-releasing hormone agonists before and during treatment with palbociclib plus fulvestrant, in line with local clinical practice.

All descriptive and numerical variables were analysed using the *IBM SPSS Statistics platform* version 26.0. Survival was assessed using Kaplan-Meier curves and survival distributions were compared using the Log-Rank Test. A *P*-value of ≤ 0.05 was used as a cutoff for statistical significance. The National Library of Medicine database (http://www.nlm.nih.gob) was used to select the articles by searching scientific terms related to breast cancer, HT, and cyclin inhibitors. The study was authorised by the Research Ethics Committee of the Principality of Asturias. Informed consent was waived due to the observational design of the study with no risk to the participants. Furthermore, the data were collected retrospectively and cover a long time period, which would have prevented the collection of informed consent from all the patients because some of them would have already died.

Results

In total, 73 patients were treated. Table 1 shows the clinicopathological data of the sample. In general, aromatase inhibitors were used in women without previous HT, and fulvestrant was used in the other patients or if aromatase inhibitors were contraindicated. Almost twice as many patients (64.4%) received palbociclib plus an aromatase inhibitor (45 letrozole and 2 exemestane) as those who received palbociclib plus fulvestrant (35.6%). Palbociclib was administered as first-line treatment in 42 patients (57.5%: 19 of them de novo and 23 after adjuvant HT), as second or subsequent-line treatment in the remaining 31 patients (42.5%), 10 (13.7%) of whom received palbociclib as at least third-line treatment.

During treatment with palbociclib plus HT, some type of toxicity was experienced by 70 patients (95.9%), reaching grade 3-4 in 52 patients (71.2%). The most frequent adverse effects were neutropenia (89%), leukopenia (74%), anaemia (63%), and thrombocytopenia (27.4%). Grade 3 neutropenia was found in 65.8% of the patients and grade 4 in 2.7% without requiring the use of granulocyte colony-stimulating factor and with no records of febrile neutropenia. The remaining haematological toxicities were mainly grade 1-2. In the absence of external causes, other common effects attributable to the combination were tiredness (13.7%), vomiting (8.2%), diarrhoea (6.8%), rash (5.5%), mucositis (5.5%), and elevated liver enzymes (4.1%). Table 2 shows further details of symptoms during treatment. Doses were decreased to 100 mg/d for 21 days in 31 patients (42.5%) and then further decreased to 75 mg/d in 16 (22%) of these patients. One patient received a starting dose of 75 mg because of her clinical characteristics. Cycle initiation was delayed in 45 patients (61.7%) and the interval between cycles was persistently > 7 days in just 2 patients (2.7%). Treatment was not discontinued because of toxicity in any patient.

During a median follow-up of 17 months, there were 21 deaths (28.8%) and 40 patients (54.8%) experienced disease progression during palbociclib treatment. A total of 52 women (71.2%) were still alive at study closure, of whom 33 (45.2%) were on active combination therapy. Estimated PFS was 22 months (95% confidence interval [95% CI]: 17.7-26.3 months) in the patients who received palbociclib plus HT as first-line treatment and 13 months (95% CI: 6.2-19.8 months) in patients who received it as subsequent-line treatment. Estimated PFS was statistically significantly longer in asymptomatic patients with ECOG 0 (22 months) (95% CI: 18.2-26.0 months) than in patients with ECOG ≥ 1 (12 months) (95% CI: 10.1-13.9 months; *P* = 0.021) (Figure 1). However, no significant differences were found in PFS by age, associated HT, or disease stage (Table 3).

Table 1. Clinicopathological characteristics of the sample

VARIABLE	N	(%)
Sex		
Male	1	1.4%
Female	72	98.6%
Age		
< 65 years	38	52%
≥ 65 years	35	48%
Functional status		
ECOG 0	34	46.6%
ECOG 1	36	49.3%
ECOG 2	3	4.1%
Menopausal status		
Premenopause	11	15.1%
Menopause	62	84.9%
Diagnostic stage		
I	13	17.8%
II	23	31.5%
III	14	19.2%
IV	23	31.5%
Prior chemotherapy		
Adjuvant/Neoadjuvant	38	52.1%
Metastatic	11	15.1%
Number of lines of previous hormone therapy		
0	19	26.0%
Adjuvant	23	31.5%
1 metastatic	21	28.8%
≥ 2 metastatic	10	13.7%
Previous hormone therapy		
Tamoxifen	41	56.2%
Aromatase inhibitors	38	52.1%
Fulvestrant	10	13.7%
Progestins	1	1.4%
Disease stage		
Distant	68	93.1%
Locoregional	1	1.4%
Distant + locoregional	4	5.5%
Disease site		
Visceral	45	61.6%
Hepatic	18	24.7%
Pulmonary	31	42.5%
Central nervous system	1	1.4%
Nonvisceral	28	38.4%
Bone alone	16	22.0%
Bone plus other	12	16.4%

ECOG: Eastern Cooperative Oncology Group.

Discussion

The study sample was heterogeneous. Patients were treated with palbociclib plus aromatase inhibitors or fulvestrant as first-line and successive treatments. The median age of patients was slightly higher than that of the PALOMA-2[7] and PALOMA-3[9] study populations: thus, the profile of patients managed in our daily practice was similar to that of patients in the FLATIRON study[15]. Fewer premenopausal women were enrolled in the present study than in other studies (PALOMA-3, MONALEESA-7, MONARCH-2)[9,16,17]. Despite this aspect, excellent functional status was maintained in 95.9% of patients with ECOG 0-1. Compared to the PALOMA-2 and PALOMA-3 study populations, a high percentage of our patients had received chemotherapy for localized disease, which represents a larger high-risk population, but relatively fewer had received chemotherapy for metastatic disease.

Table 2. Adverse effects and grade

TOXICITY	N	(%)
Neutropenia	**65**	**89.0%**
Grade 4	2	2.7%
Grade 3	48	65.8%
Grade 2	12	16.4%
Grade 1	3	4.1%
Leukopenia	**54**	**74.0%**
Grade 4	1	1.4%
Grade 3	11	15.1%
Grade 2	31	42.5%
Grade 1	11	15.1%
Anaemia	**46**	**63.0%**
Grade 4	0	0.0%
Grade 3	2	2.7%
Grade 2	10	13.7%
Grade 1	34	46.6%
Thrombopenia	**20**	**27.4%**
Grade 4	3	4.1%
Grade 3	2	2.7%
Grade 2	1	1.4%
Grade 1	14	19.2%
Tiredness	**10**	**13.7%**
Grade 4	0	0.0%
Grade 3	2	2.7%
Grade 2	2	2.7%
Grade 1	6	8.2%
Upper respiratory tract infection	**8**	**10.0%**
Grade 4	0	0.0%
Grade 3	2	2.7%
Grade 2	4	5.5%
Grade 1	2	2.7%
Vomiting	**6 (G1)**	**8.2%**
Diarroea	**5**	**6.8%**
Grade 2	1	1.4%
Grade 1	4	5.5%
Mucositis	**4**	**5.5%**
Grade 2	3	4.1%
Grade 1	1	1.4%
Elevated liver enzymes	**3**	**4.1%**
Grade 2	2	2.7%
Grade 1	1	1.4%
Rash	**4 (G2)**	**5.5%**
Nasopharyngitis	**3**	**4.1%**
Grade 2	1	1.4%
Grade 1	2	2.7%
Constipation	**2 (G2)**	**2.7%**
Dry Skin	**2 (G1)**	**2.7%**
Tiredness	**1 (G1)**	**1.4%**
Alopecia	**1 (G2)**	**1.4%**
Headache	**1 (G1)**	**1.4%**
Dyspnea	**1 (G2)**	**1.4%**
Insomnia	**1 (G1)**	**1.4%**
Dizziness	**1 (G1)**	**1.4%**

Table 3. Correlation between progression-free survival and clinical variables

VARIABLE (N)	PFS, mo (median; 95% CI)	*Log rank* (chi-squared; *P*)
Age		
< 65 years (38)	15 (9.3-20.7)	1.133
≥ 65 years (35)	24 (11.8-36.2)	P = 0.287
Functional status		
ECOG 0 (34)	22 (18.2-25.9)	**5.350**
ECOG ≥ 1 (39)	12 (10.1-13.9)	**P = 0.021**
Associated hormone therapy		
Aromatase inhibitors (47)	21 (3.4-14.4)	0.116
Fulvestrant (26)	19 (N/C)	P = 0.734
Visceral disease		
Yes (45)	21 (12.8-29.2)	0.007
No (28)	15 (5.1-25)	P = 0.931
Bone disease alone		
Yes (16)	15 (N/C)	0.31
No (57)	19 (11.5-265)	P = 0.861

95% CI: 95% confidence interval; N/C: not calculated; PFS: progression-free survival.

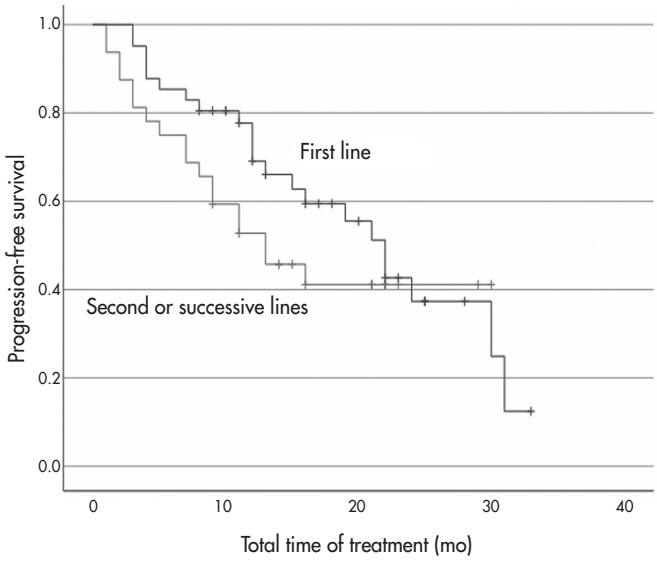
The percentage of patients treated with prior HT was similar to that reported in previous studies and the same as that reported in the PALOMA-3 study. Almost 2 out of 3 patients had visceral disease at the start of treatment. It is noteworthy that more patients had pulmonary involvement than those in other studies; on the other hand, liver involvement was higher in patients in the PALOMA-3 study than in our study. Previous real-life studies, such as FLATIRON, have reported similar results. However, the presence of visceral disease does not seem to have influenced functional status at the start of treatment or long-term prognosis (Table 1).

Interestingly, the rate of haematological toxicity, mainly leukopenia and neutropenia, was higher than that reported in the PALOMA-2 and PALOMA-3 studies. However, few patients had grade 4 neutropenia and there were no episodes of febrile neutropenia. There were fewer documented nonhaematological toxicities in our study than in the pivotal studies (Table 2). Treatment delays were frequent and similar to those reported in the PALOMA-2[7] and PALOMA-3[9]. Dose adjustments were also frequent but higher than those reported in the published studies. Nevertheless, these aspects do not seem to have had an impact on treatment effectiveness.

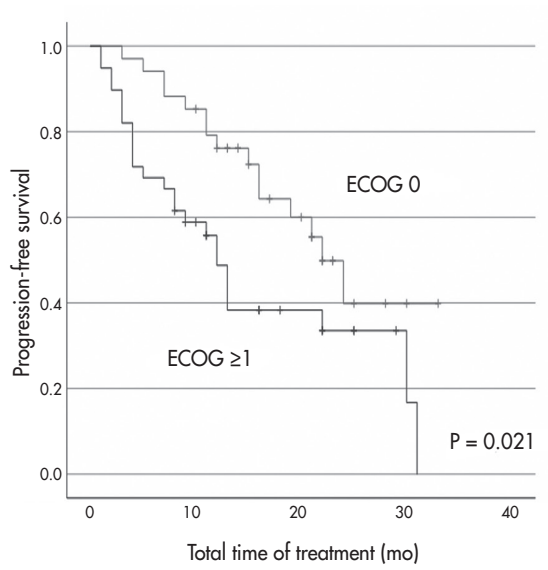
In our study, patients receiving first-line palbociclib had PFS of 22 months, which was similar to that observed in the PALOMA-2 study. Of the 42 patients included in this group, only 5 received fulvestrant, and so it is unlikely that this aspect would have had a significant impact on the survival data. This subgroup of patients was included in the MONALEESA-3 and GEICAM/2014-12 (FLIPPER) studies, in which PFS was 20.5 months[18] and 31.8 months[19], respectively. On the other hand, PFS was 13 months in women receiving palbociclib as second or subsequent-line treatment. This result was slightly longer than that of 2nd-line treatment in the PALOMA-3[9] study.

The type of HT used with palbociclib does not seem to have influenced the survival results. However, given the small sample size and the retrospective observational study design, we cannot draw solid conclusions about the best combination therapy. We can confirm that functional status at the start of treatment, as measured by ECOG performance status scores, remains a prognostic factor for survival: PFS was significantly better in asymptomatic patients than in the other patients (ECOG 0 at 22 months vs ECOG ≥ 1 at 12 months). Visceral disease at the start of treatment did not affect survival in our patients. It has been shown that the presence of metastases beyond bone or lymph node involvement does not detract from the benefit of adding CDK4/6 inhibitors to HT[7,9]. This finding has been confirmed in previous studies (PALOMA-2, PALOMA-3).

Figure 1. *Progression-free survival by line of treatment and functional status.*



Progression-free survival in patients on first-line treatment at 22 months (95% CI: 17.7-26.3 months; N = 42) and second-line or successive treatment at 13 months (95% CI: 6.2-19.8 months; N = 31).



Progression-free survival by functional status at 22 months ECOG 0 (95% CI: 18.2-26.0 months; N = 34) vs at 12 months ECOG ≥ 1 (95% CI: 10.1-13.9 months; P = 0.021; N = 39).

CI: confidence interval; ECOG: *Eastern Cooperative Oncology Group performance status.*

This study has relevant limitations: for example, fewer patients were enrolled than in previous real-life studies[15,20]. Our sample was heterogeneous in terms of when palbociclib was used during the course of the disease, and included women receiving de novo, first-line, and successive lines of treatment, all of which affects survival outcomes. Selection bias may have affected the results due to having only included patients who could be followed-up. Furthermore, we did not conduct a multivariate analysis of mortality or one adjusted for lines of treatment. Although we are unable to offer solid conclusions on effectiveness, we can at least establish hypotheses on the incorporation of CDK4/6 inhibitors in the treatment of luminal metastatic breast cancer. The 17-months of follow-up provided indicative data on PFS: longer follow-up would provide data on overall survival. We confirm that aspects such as age or visceral involvement do not limit the use of cyclin inhibitors in patients with luminal cancer, and that the time at which they are used appears to be more relevant than the type of HT with which they are combined. This study also confirms that although the most common adverse effects are haematological, they are easy to manage and do not affect continuation of treatment.

Our results are in line with those of other ongoing multicentre and international collaborative projects, such as the Ibrance Real World Insights (IRIS) study. They show that palbociclib plus HT is an effective treatment for advanced luminal breast cancer with an acceptable toxicity profile. This treatment can be administered at different times during the course of metastatic disease in heterogeneous groups of patients.

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Conflict of interests

No conflict of interest.

Contribution to the scientific literature

No study has been published in Spain that has the same characteristics as this study. Most of the published studies have been conducted in ideal situations and under optimal conditions. Studies based on real-life data provide post-marketing evidence on drug effectiveness and safety. Results show that palbociclib plus hormone therapy for advanced luminal breast cancer appears to be an effective treatment, has an acceptable toxicity profile, and can be administered at different times over the course of metastatic disease in a heterogeneous group of patients.

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