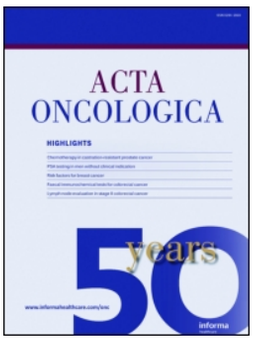

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ORIGINAL ARTICLE

Efficacy and safety of cyclin dependent kinases 4/6 inhibitors in the treatment of metastatic breast cancer: a real-world experience

Luisa Edman Kessler[a,b]*, Oscar Wiklander[a,c]*, Eva Hamberg[b], Jonas Bergh[a,b], Theodoros Foukakis[a,b] and Alexios Matikas[a,b]

[a]Department of Oncology/Pathology, Karolinska Institutet, Stockholm, Sweden; [b]Breast Center, Theme Cancer, Karolinska University Hospital, Stockholm, Sweden; [c]Department of Laboratory Medicine, Karolinska Institutet, Stockholm, Sweden

ABSTRACT

Background: Randomized trials have shown survival gains for patients with metastatic breast cancer (BC) treated with CDK4/6 inhibitors (CDK4/6i) in combination with endocrine agents. It is not unlikely that there may be discrepancies between the generally fit clinical study population and the real-world setting that could affect adherence to treatment guidelines, tolerance to treatment and outcome.

Material and methods: Consecutive patients with metastatic or locally advanced and unresectable BC that were treated between July 2017 and January 2020 at Karolinska University Hospital, Stockholm, Sweden and that had received at least one dose of CDK4/6i were included in this retrospective study. The primary endpoint was safety, including toxicity according to CTCAE 5 and rates of treatment interruptions, dose reductions and discontinuations. The secondary endpoint was efficacy based on the treating physicians' assessments in terms of progression free (PFS) and overall survival (OS), as well as the factors associated with patient outcome.

Results: Eighty-eight patients were included in the analysis, with a median age of 67.2 years. Grade 4 neutropenia occurred in 9.1% of patients and one episode of neutropenic infection was observed. Dose reductions were made in 38.6% of patients, while 11.4% discontinued treatment due to toxicity, most commonly non-hematologic. After a median follow-up of 18.33 months, median PFS was 13.30 months (95% CI, 11.39–15.21) and median OS could yet not be estimated. In multivariable analysis, number of prior chemotherapy lines was an independent predictor for shorter PFS (HR = 3.28, 95% CI 1.50–7.16, $p = .003$).

Conclusions: CDK4/6i administered in a real-world setting exhibits a similar toxicity profile but higher incidence of treatment discontinuation compared to randomized trials. Efficacy of CDK4/6i among patients pretreated with multiple therapy lines is markedly reduced.

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Introduction

Although endocrine therapy is considered as the standard of care for initial treatment of hormone receptor (HR) positive, Human Epidermal Growth Factor Receptor 2 (HER2) negative metastatic breast cancer (MBC), development of resistance through diverse mechanisms is eventually inevitable [1]. The most successful agents employed to delay or circumvent resistance are cyclin dependent kinases 4/6 inhibitors (CDL4/6i), whose use in combination with endocrine therapy has been associated with striking prolongation of progression free survival (PFS) but even gains in overall survival (OS) compared to endocrine therapy alone [2–5], an effect not previously demonstrated with other molecularly targeted agents [1]. At the same time, randomized trials have shown that the main dose-limiting toxicity leading to dose reductions and treatment interruptions or discontinuations is the suppression of myeloid progenitors, manifesting itself mainly as neutropenia [6]. However, the overall risk for infections is low and these agents are generally considered to be well-tolerated, despite clinically significant non-hematologic adverse events such as QTc prolongation mainly due to ribociclib, gastrointestinal toxicity due to abemaciclib, liver toxicity and, rarely, interstitial lung disease [7].

Although evidence based on data from randomized trials is the gold standard through which the benefit derived from new agents should be judged [8], its translation to clinical practice can sometimes be challenging. In the first- and second-line CDK4/6i trials, the majority of patients were treatment naïve or had progressed after at most one chemotherapy line, while the majority of patients allocated to the control groups never received CDK4/6i at a later therapy line. On the other hand, available data from real-world settings demonstrate decreased efficacy of CDK4/6i among heavily pretreated patients compared with outcomes reported in prospective trials [9,10], which implies that patient selection

CONTACT Alexios Matikas alexios.matikas@ki.se Breast Center, Theme Cancer, Karolinska University Hospital, Gävlegatan 55, Stockholm, 171 64, Sweden
*These authors contributed equally.

may be a major driver behind reported outcomes from clinical trials. In addition, adherence to dose modification guidelines within clinical trials is presumably higher compared to the use of novel agents in routine practice, with the prognostic implications being largely unexplored.

Considering the aforementioned limitations of prospective trials and the scarcity of available data concerning efficacy and safety of CDK4/6i at later lines, we conducted a retrospective analysis of the use of CDK4/6i in a real-world clinical setting from the Swedish environment in an effort to complement the available evidence.

Methods

Study design and population

This is a retrospective cohort study whose objective was to evaluate the safety and efficacy of CDK4/6i in the treatment of MBC at a real-world setting. Consecutive patients with metastatic or locally advanced and unresectable BC that were treated between July 2017 and January 2020 at Breast Center (earlier known as Oncology Department, Radiumhemmet), Karolinska University Hospital, Stockholm, Sweden and that had received at least one dose of CDK4/6i were identified and included in the study. No other inclusion or exclusion criteria were used. Demographic and clinicopathologic data regarding tumor characteristics (hormone receptor and HER2 status at the primary and the metastatic disease), prior treatments at the neoadjuvant and adjuvant setting and any prior treatment for MBC, and efficacy and safety of the CDK4/6i-based treatment were extracted from the electronic patient charts independently by two investigators (LEK and OW). In addition, data on comorbidities were extracted from the codified diagnoses available from the patient charts. Discrepancies were discussed with a third investigator (AM) and consensus was reached in all cases. This non-interventional retrospective study was approved by the responsible ethics committee at Karolinska Institutet (decision number 2019-01872).

Endpoints

The first endpoint of this retrospective study was the safety of CDK4/6i-based treatment as assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, with a focus on hematologic toxicity. In addition, information regarding treatment interruption, dose reduction and treatment discontinuation as well as the causes to treatment modifications was collected. The second endpoint of the study was the efficacy of CDK4/6i for the treatment of locally advanced unresectable, or metastatic BC. Objective response rate (ORR), defined as the sum of patients achieving either a complete (CR) or a partial response (PR) as best radiologic response, was based on the treating physician's assessment carried out in accordance with local practice every approximately three months and which was in line with the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [11]. PFS was defined as the time from treatment start to disease progression or death, whichever occurred first. OS was defined as the time from treatment start until death by any cause.

Statistical analysis

This was a retrospective analysis of the usage of CDK4/6i in a single tertiary center. Summary tables (descriptive statistics and/or frequency tables) were provided for all baseline and efficacy variables, as appropriate. Continuous variables were summarized with descriptive statistics (n, median and range). Time-to-endpoint events (PFS, OS) were estimated using the Kaplan–Meier method and the comparisons were computed with the log-rank test. Times for event-free patients at the time of data cutoff (April 8th 2020) in all survival analyses were calculated from the date of treatment start to the date of last follow-up. The association between prognostic factors and survival was examined using Cox proportional hazards regression model. Clinical variables that were included in the models as covariates were age, comorbidities, best response to CDK4/6i, site of metastasis, endocrine sensitivity, number of prior chemotherapy lines for metastatic disease and PR status at metastasis. An arbitrary level of 5% statistical significance (two-tailed) was used. IBM SPSS Statistics version 25.0 (SPSS Inc., Chicago, IL, USA) and GraphPad Prism version 8.4 (GraphPad Software Inc., La Jolla, CA, USA) were used to perform the statistical analyses.

Results

Patient characteristics

In total, 88 patients were identified and included in the analysis with a median age of 67.2 years (range, 32.2–86.3). Approximately two thirds of patients had at least one comorbidity (range, 0–4). Histological confirmation of recurrence to a distant site was obtained from 82 patients (93.1%), with 81 (92.0%) being ER-positive and 5 (5.7%) HER2-positive. All patients were ER-positive either at the primary tumor or the metastatic biopsy. Only two patients (2.3%) had *de novo* metastatic disease; 69 patients (78.4%) had received adjuvant endocrine therapy, of which 42 relapsed during its duration or within 12 months after its completion. The median number of prior endocrine therapy lines for metastatic disease was 1 (range, 0–5) and the median number of prior chemotherapy lines was also 1 (range, 0–5). The patients' demographic and clinicopathologic characteristics, as well as information regarding previous treatments at the neoadjuvant, adjuvant and metastatic settings are presented in Table 1.

Exposure to CDK4/6 inhibitors and safety

Palbociclib was the CDK4/6i of choice in more than two thirds of patients (60 patients; 68.2%) and ribociclib was used in the remaining ones. CDK4/6i was started on a reduced dose in 7 patients (8.0%), with the rest starting on the full recommended dose. The most common endocrine

Table 1. Patient demographic and clinicopathologic characteristics.

	All patients $N = 88$ (%)
Age	
Median (min–max)	67.2 (32.2–86.3)
$\leq$ 70 years	51 (58.0)
$>$ 70 years	37 (42.0)
Menopausal status	
Premenopausal	11 (12.5)
Perimenopausal	2 (2.3)
Postmenopausal	65 (73.9)
Unknown	10 (11.3)
Number of comorbidities	
0	32 (36.4)
1	29 (33.0)
2	18 (20.5)
3 or more	9 (10.3)
Type of comorbidities	
Hypertension	27 (30.7)
Cardiovascular disease	16 (18.2)
Respiratory disease	2 (2.3)
Psychiatric conditions	22 (25.0)
Other	16 (18.2)
Estrogen Receptor at primary disease	
Positive	82 (93.2)
Negative	2 (2.3)
Unknown	4 (4.5)
Progesterone Receptor at primary disease	
Positive	59 (67.0)
Negative	20 (22.7)
Unknown	9 (10.2)
HER2 at primary disease	
Positive	7 (8.0)
Negative	62 (70.5)
Unknown	19 (21.6)
Neoadjuvant and/or adjuvant chemotherapy	
Anthracycline and taxane	34 (38.6)
Anthracycline only	22 (25.0)
Other	3 (3.4)
None	29 (32.9)
Adjuvant endocrine therapy	
Aromatase Inhibitor	30 (34.1)
Tamoxifen	33 (37.5)
Both	4 (4.5)
None	18 (20.5)
Unknown	3 (3.4)
Time from adjuvant endocrine to relapse	
Relapse during treatment or $<$ 12 months since its completion	42 (47.7)
Relapse $\geq$ 12 months since its completion	27 (30.7)
Unknown	19 (21.6)
Type of relapse	
Local/locoregional unresectable	4 (4.5)
Metastatic	82 (93.2)
De novo metastatic disease	2 (2.3)
Sites of metastatic disease	
Bone and/or nodal metastases	30 (34.1)
Visceral metastases with or without bone/nodal disease	53 (60.2)
Brain metastases with or without systemic disease	2 (2.3)
Unknown	3 (3.4)
Estrogen Receptor at metastasis	
Positive	81 (92.0)
Negative	1 (1.1)
Unknown	6 (6.8)
Progesterone Receptor at metastasis	
Positive	37 (42.0)
Negative	36 (40.9)
Unknown	15 (17.0)
HER2 at metastasis	
Positive	5 (5.7)
Negative	69 (78.4)
Unknown	14 (15.9)
Number of endocrine lines prior to CDK4/6 inhibitor	
Median (range)	1 (0–5)
0	10 (11.4)
1	44 (50.0)
2	20 (22.7)
3 or more	14 (15.9)
Type of prior endocrine lines	
Anastrozole and letrozole	60 (68.2)
Exemestane	14 (15.9)
Tamoxifen	24 (27.2)
Fulvestrant	12 (13.6)
Unknown	10 (11.3)
Number of chemotherapy lines prior to CDK4/6 inhibitor	
Median (range)	1 (0–5)
$<$ 3 prior lines	68 (77.3)
$\geq$ 3 prior lines	20 (22.7)

therapy combined with CDK4/6i was fulvestrant (62 patients; 70.5%), followed by anastrozole/letrozole (17 patients; 19.3%) and exemestane (9; 10.2%).

At least one dose reduction was performed in 34 patients (38.6%) after a median of 3.5 cycles (range, 2–21), most commonly due to hematologic toxicity (70.5% of cases), followed by fatigue and/or decrease in performance status (11.7% of cases). A second dose reduction was performed in 10 patients (11.4%). In addition, at least one treatment interruption was needed in the majority of patients (68; 77.3%) after a median of 2 cycles (range, 1–16), most commonly due to hematologic toxicity (64.7% of cases). In 4 patients, treatment was interrupted due to reasons not related with toxicity. Finally, treatment was discontinued due to toxicity or other serious events in 10 patients (11.4%): 2 cases of kidney injury manifesting as decreased glomerular filtration rate (both ribociclib), 2 cases of skin toxicity (both palbociclib) and 1 case each of hepatotoxicity (ribociclib), prolonged QTc time (ribociclib), peptic ulcer (ribociclib), pathologic hip fracture (palbociclib), thrombocytopenia (palbociclib), and neutropenia (palbociclib). Treatment interruption, dose reduction or early discontinuation due to toxicity were not associated with PFS or OS.

The most common grade 3/4 adverse event of interest was neutropenia (8 patients; 9.1%) which first occurred after a median of 2 cycles (range, 1–5), followed by thrombocytopenia (2 patients; 2.3%). Non-neutropenic infections that were treated with antibiotics and required treatment interruption and/or admission to the hospital were more common compared to neutropenic infections, 18.2% versus 2.3%.

Treatment efficacy

Nine patients did not have evaluable data for radiologic response at the time of data cutoff. Out of the remaining 79 patients, no patient achieved a complete remission and 21 had a partial response to treatment, an ORR of 26.5% according to routine radiology reports. Furthermore, 49 patients had stable disease as best response while 9 patients (11.3%) had disease progression. After a median follow-up of 18.33 months (95% CI, 14.05–22.60), 26 (29.5%) patients had died, 25 (28.4%) had progressed on CDK4/6i but were still alive and the remaining 37 (42%) were still on CDK4/6i treatment. The median PFS was 13.30 months (95% CI,

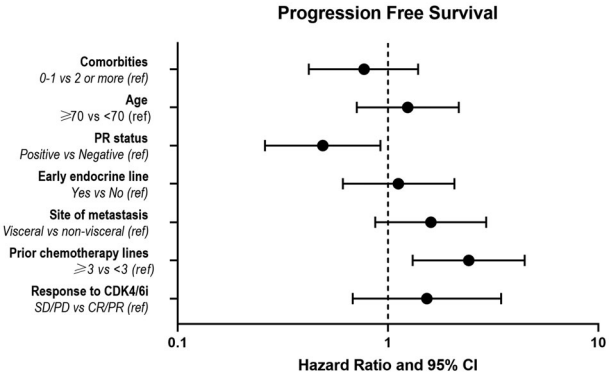

Figure 1. Forest plot of Hazard Ratio for progression free survival, Cox regression univariate models. PR: progesterone receptor; CDK4/6i: cyclin dependent kinases 4/6 inhibitor; SD: stable disease; PD: progressive disease; CR: complete response; PR: partial response; CI: confidence interval. Early endocrine line was defined as relapse at least 12 months after the completion of adjuvant endocrine therapy and at most one endocrine line for metastatic disease. Response refers to best radiologic response.

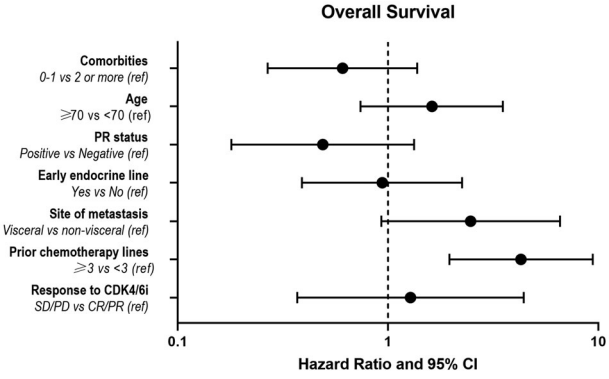

Figure 2. Forest plot of Hazard Ratio for overall survival, Cox regression univariate models. PR: progesterone receptor; CDK4/6i: cyclin dependent kinases 4/6 inhibitor; SD: stable disease; PD: progressive disease CR: complete response; PR: partial response; CI: confidence interval. Early endocrine line was defined as relapse at least 12 months after the completion of adjuvant endocrine therapy and at most one endocrine line for metastatic disease. Response refers to best radiologic response.

11.39–15.21) and the median OS could not be estimated. The probability of survival at one year was 82.2%.

Univariate Cox regression analysis of factors associated with PFS and OS are shown in Figures 1 and 2, respectively. Prior receipt of at least three chemotherapy lines for metastatic disease, regardless of number of endocrine therapy lines, was an independent predictor for shorter PFS (HR = 3.28, 95% CI 1.50–7.16, $p = .003$; Figure 3) and OS (HR = 6.97, 95% CI 2.27–21.42, $p < .001$) when adjusted for age, comorbidities, best response to CDK4/6i, site of metastasis, endocrine sensitivity and PR status at metastasis. The median PFS under treatment with a CDK4/6i of patients that had previously received fewer than three chemotherapy lines was 14.73 months (95% CI 10.86–18.59) compared with 7.66 months (0.05–15.27) for those treated with three or more chemotherapy lines ($p = .003$; Figure 4).

Discussion

Over the last five years, three CDK4/6i have been approved for treatment of MBC. Several randomized clinical trials

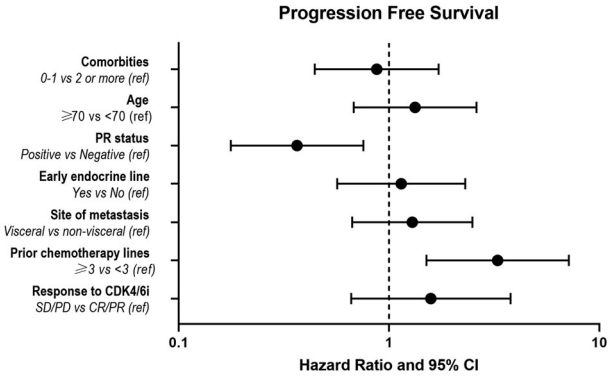

Figure 3. Forest plot of Hazard Ratio for progression free survival, Cox regression multivariable model. PR: progesterone receptor; CDK4/6i: cyclin dependent kinases 4/6 inhibitor; SD: stable disease; PD: progressive disease CR: complete response; PR: partial response; CI: confidence interval. Early endocrine line was defined as relapse at least 12 months after the completion of adjuvant endocrine therapy and at most one endocrine line for metastatic disease. Response refers to best radiologic response.

(palbociclib: the PALOMA studies, ribociclib: the MONALEESA studies, and abemaciclib: the MONARCH studies) have demonstrated that they are generally safe and well tolerated and, importantly, improve both PFS [12–15] and OS [3–5] in HR-positive/HER2-negative MBC. Nevertheless, real-world studies are still relevant due to differences in patient population compared with that of clinical trials – more heterogeneous and unselected, including older patients although available evidence show similar efficacy in this group [16], patients with more advanced disease and with baseline comorbidities [17]. As an example, the median patient age in this study was 8 and 10 years higher than MONARCH-2 and PALOMA-3, respectively [18,19]. Here, we add to the existing literature with a retrospective cohort study that evaluates CDK4/6i, with both safety and efficacy being in line with clinical trial data but also with several important findings. Firstly, a metastatic biopsy was available in 93.1% of patients. In contrast, a biopsy in the metastatic setting was recommended but not compulsory in many of the previous phase 3 trials. For example, in PALOMA-3, a metastatic biopsy was obtained from 60% of the patients [15]. This ignores the well-known phenomenon of receptor conversion during metastatic progression [20] and the recommendation from contemporary guidelines to obtain a metastatic biopsy [21], and implies that at least some of the rapid progressors in clinical trials may have had HR-negative MBC. In addition, in our study only 2.3% of patients had *de novo* metastatic disease, roughly similar to population-based studies [22,23]. In previous first line trials with CDK4/6i, patients with *de novo* metastatic disease ranged between 34.1% to 41% [12–14]. These patients are completely endocrine naïve, skewing outcomes in both the control and intervention groups. These observations demonstrate the practical value of real-world studies in offering complementary information that prospective randomized trials might not capture.

Limited available data in heavily pretreated patients indicate lower efficacy of CDK4/6i [9,10]. Here we demonstrate that prior receipt of at least three chemotherapy lines was an independent predictor of worse outcomes, thus supporting the use of CDK4/6i earlier in the disease trajectory. This

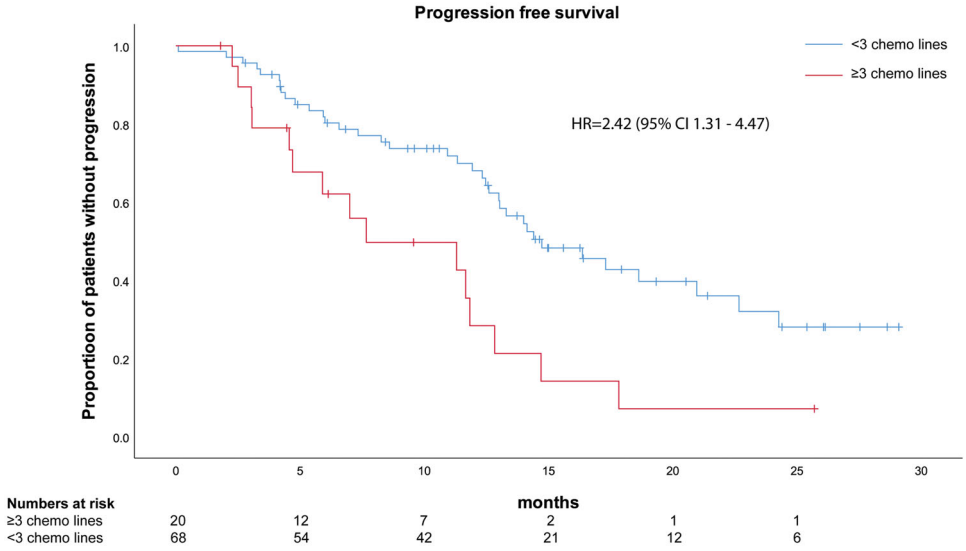

Figure 4. Kaplan–Meier curve for progression free survival under CDK4/6 inhibitor, for patients previously treated with up to 3 chemotherapy lines (blue curve) compared with patients previously treated with 3 or more chemotherapy lines (red curve). HR: hazard ratio; CI: confidence interval.

observation is supported by data from studies of CDK4/6i in combination with fulvestrant following progression on an aromatase inhibitor, although cross-trial comparisons are inherently hazardous: median PFS in MONARCH-2 was 16.9 months, compared with 9.5 months in PALOMA-3 [5,15]. The latter population was more pretreated, with one third receiving at least 2 treatment lines for MBC including one third receiving 1 chemotherapy line, whereas in the former trial no prior chemotherapy and up to 1 endocrine line was allowed. Although lower CDK4/6i efficacy due to decreased endocrine addiction following multiple endocrine lines is the most probable explanation, the mechanism through which prior chemotherapy lines modulate response to CDK4/6i is unclear. A highly speculative theory is based on the non-mechanistic effects of CDK4/6i, which have been shown to promote anti-tumor immunity through increased tumor cell antigen presentation and anti-tumor T-cell response [24]. This might be an important pathway through which CDK4/6i exert their anticancer effect and, in the presence of advanced malignancies and exhausted anti-tumor immunity, CDK4/6i are unable to elicit anti-tumor responses.

Safety was generally in line with prospective trials. Dose reduction at least once was seen in about one third of the patients, which was similar to (34% in PALOMA-3 and 35% in MONALEESA-7) or somewhat lower than (46.5% in MONARCH-3) previous trials. Treatment discontinuation due to toxicity was seen in 11.4% of patients. This is considerably higher than observed in previous clinical trials with the CDK4/6i used here (4% in PALOMA-3, 4% in MONALEESA-7), but lower than reported for abemaciclib (25.1% in MONARCH-3). This finding may reflect the study population's heterogeneity, with some patients being heavily pretreated with up to five previous chemotherapy lines, thus being less fit and with a poorer performance status at baseline. However, this could also suggest a non-adherence to treatment guidelines, with treatment being discontinued too early or incorrectly by treating physicians. Interestingly, no effect on PFS or OS was seen by treatment interruption, dose reduction or treatment discontinuation.

On the other side, this is a retrospective single-center cohort study, prone to information bias and data missingness, as well as to bias from the non-standardized response assessments and intervals for imaging studies. Furthermore, the small sample size may have led to chance findings or masked correlations, thus affecting the results. In addition, no efficacy comparisons can be made with randomized clinical trials due to different study populations and our results should only be considered as suggestive of the effect of prior chemotherapy lines to CDK4/6 inhibition. Finally, the generalizability of our findings is mitigated by the fact that patients were treated at the same highly specialized cancer center.

Conclusion

In conclusion, CDK4/6i used in the real-world setting display a similar toxicity profile but higher incidence of treatment discontinuation compared to randomized clinical trials. Efficacy was significantly lower among heavily chemotherapy-pretreated patients.

Disclosure statement

Luisa Edman Kessler, Eva Hamberg and Alexios Matikas have no conflicts of interest to disclose. Oscar Wiklander is consultant for and has equity interests in Evox Therapeutics Ltd., Oxford, UK. Jonas Bergh reports that his institution (Karolinska Institutet and/or Karolinska University Hospital) has received commercial research grants from AstraZeneca, Amgen, Bayer, Roche, Merck, Pfizer and Sanofi Aventis. No personal payments. Payment from UpToDate for a chapter in breast cancer prediction paid to Asklepios Medicine HB. Theodoros Foukakis: institutional grants from Roche and Pfizer and personal fees from Novartis, Pfizer, Roche and UpToDate.

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ORCID

Oscar Wiklander http://orcid.org/0000-0003-1176-8114

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