BMC Cancer

RESEARCH Open Access

# Activity of CDK4/6 inhibitors and parameters affecting survival in elderly patients in age-subgroups: Turkish Oncology Group (TOG) retrospective study

Seda Kahraman[1*], Mutlu Hizal[1], Burcin Cakan Demirel[2], Deniz Can Guven[3], Ozge Gumusay[4], Basak Oyan Uluc[4], Ertugrul Bayram[5], Burcu Gulbagci[6], Alper Yasar[7], Sena Ece Davarci[8], Eda Eylemer Mocan[9], Omer Acar[10], Deniz Isik[11], Esra Aydin[12], Yusuf Karakas[13], Melike Ozcelik[14], Murat Keser[15], Sadi Kerem Okutur[16], Onder Eren[17], Serkan Menekse[18], Dincer Aydin[19], Funda Yilmaz[20], Ozlem Dogan[21], Gulhan Ozkanli[22], Hakan Yucel[23], Veli Sunar[24], Musa Baris Aykan[25], Ozlem Ozdemir[26], Berna Bozkurt Duman[27], Merve Keskinkilic[28], Teoman Sakalar[29], Ali Inal[30], Muge Karaoglanoglu[31], Asude Aksoy[32], Muhammed Muhiddin Er[33], Nazim Serdar Turhal[34], Nurhan Onal Kalkan[35] and Mehmet Ali Nahit Sendur[1]

## Abstract

Highly selective inhibitors of cyclin-dependent kinase 4 and 6 (CDK4/6is) have emerged as a standart of care for first- and second-line therapies in combination with endocrine therapy (ET) for HR+/HER2- metastatic breast cancer (MBC) patients. It has been reported that combination therapy is more effective than ET alone and is safe in elderly patients as well as young patients. Nevertheless, elderly and very old patients with HR+/HER2-MBC treated with CDK4/6 inhibitor (CDK4/6i) combinations are relatively underrepresented in randomized controlled trials. To contribute to the literature, we investigated the real-world efficacy, factors associated with survival and the rates of adverse events (AEs) of the treatment with palbociclib or ribociclib plus ET in the HR+/HER2- MBC patient cohort over the age of 65 for age subgroups. In this retrospective study, 348 patients were divided into subgroups: 65–69 years old, 70–79 years old and 80 years and older. Median PFS (mPFS) for whole group was 18.3 (95% CI,14.3–22.3) months. There was no significant difference in mPFS between age groups ($p=0.75$). The estimated median OS (mOS) was 39.5 (95% CI, 24.9–54.1) months and there was no significant difference between age groups ($p=0.15$). There was a meaningfull numerical difference that did not reach statistical significance in patients who received CDK4/6i treatment as the first line for MBC. Grade 3–4 AEs were reported in 42.7% for the entire group, and neutropenia was the most common (37.3%). It can be concluded that combination therapy with palbociclib or ribociclib with an ET partner has similar efficacy and is safe among subgroups of older patients diagnosed with HR+/HER2-MBC.

*Correspondence:
Seda Kahraman
sedakayacan.kahraman@gmail.com

Full list of author information is available at the end of the article

**Keywords** CDK 4/6 inhibitors, Metastatic breast cancer, Geriatric population

## Introduction

The hormone receptor-positive and HER2-negative (HR+/HER2-) breast cancer subgroup accounts for more than half of metastatic breast cancer (MBC) patients. As the primary treatment for HR+/HER2- MBC patients, highly selective inhibitors of cyclin-dependent kinase 4 and 6 (CDK4/6is) have paved the way for first- and second-line therapies in combination with endocrine therapy (ET) partner. In pivotal studies, three CDK4/6i drugs in combination with ET have been reported to be safe and effective in terms of mPFS compared to ET alone, including in the elderly patient group [1–3].

Elderly and very old patients with HR+/HER2- MBC treated with CDK4/6is are relatively less represented in randomized controlled trials (RCTs), therefore our current knowledge comes from the meta-analysis or pooled analysis of RCTs and retrospective studies [4–8].

This study aims to evaluate the real-world efficacy and safety of treatment with CDK4/6is in elderly subgroups of patients with HR+/HER2- MBC. We investigated the factors associated with survival and the rates of adverse events (AEs) of the treatment with palbociclib or ribociclib plus ET (letrozole or fulvestrant) in the HR+/HER2- MBC patient cohort over the age of 65 for age subgroups.

## Materials and methods

In our study, patients who were treated with the combination of palbociclib or ribociclib and letrozole or fulvestrant for MBC between November 2017 and April 2022 were included. 44 tertiary oncology centers contributed data to the study. Patients aged 65 and over were included in the study as the elderly patient group, and these patients were divided into subgroups as 65–69 years old, 70–79 years old and 80 years and older. The demographic, clinical and pathological data of these patients were collected and recorded retrospectively from the hospital database.

In terms of CDK4/6is preference, patients treated with ribociclib and palbociclib were included because both of them reimbursed and started to be used concurrently in our country. Included patients required to have histopathologically proven ER ≥ 10% ER-positive and/or PR-positive tumor, in order to meet the drug reimbursement condition.

No inclusion or exclusion criteria were selected based on concomitant diseases of patients. Patients who were considered not to have any contraindications to combination therapy with CDK4/6i and ET due to any medical condition (i.e. comorbidity, organ failure) and patients who were able to receive at least 1 dose of the treatment are included. There was no removal from the database after patient data were collected from the centers.

Median progression-free survival (mPFS) and overall survival (mOS) of the patients were calculated with the Kaplan-Meier method. Various clinical features were tested in a univariate analysis using Kaplan-Meier method and evaluated by Log-rank analysis. The p values < 0.05 was considered statistically significant. Multivariate analysis was performed using the Cox regression technique, including both variables with $p < 0.01$ in the univariate model and covariates that might interact with survival, and hazard ratios (HRs) of progression were calculated with 95% confidence intervals. The chi-square test was used to analyze differences in clinical features among the groups. SPSS Statistics version 26.0 was utilized for data analysis. Initial response to treatment with CDK4/6i was noted according to current Response Evaluation Criteria In Solid Tumors (RECIST) criteria and was evaluated by comparing PET/CT findings for bone-only metastatic cases. Adverse events reported were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

We conducted this study according to the Declaration of Helsinki. The study protocol was approved by local ethics committee of Ankara Bilkent City Hospital as a multicenter retrospective observational study. The requirement to obtain informed consent was waived by our institutional review board because no experimental procedures were performed on the patients and medical records were used to evaluate study data. The preparation of the article was followed in accordance with the STROBE guidelines.

## Results

A total of 348 patients, 2% of whom were male, were included in this study. Median age was 71 years (range 65–86) and patients were grouped as 65–69 years old ($n = 150$), 70–79 years old ($n = 159$) and 80 years and older ($n = 39$) (group 1,2,3 respectively). At least one comorbid disease was present in 74.5% of the patients. Bone-only disease was present in 35.7% of the patients. 41.8% of patients had received systemic therapy for MBC before CDK4/6i plus ET combination. Patient characteristics are detailed in Table 1.

There was no significant difference in regard to the number and general localization of sites of metastases or the ratio of bone-only disease to visceral metastasis

**Table 1** General characteristics of the patients

| | Total *N*: 348 | *P* value |
|---|---|---|
| Age, median (range) | 71 (65–86) | 0.75 |
| Gender | | 0.83 |
| Female | 341 | |
| Male | 7 | |
| ECOG PS | | 0.35 |
| 0 | 95 | |
| 1 | 172 | |
| ≥ 2 | 57 | |
| PR | | 0.54 |
| Negative | 35 (20.1%) | |
| Positive | 139 (79.9%) | |
| CDK 4/6 inhibitor combined with ET | | **0.024** |
| Palbociclib plus letrozole | 100 (28.7%) | |
| Palbociclib plus fulvestrant | 78 (22.4%) | |
| Ribociclib plus letrozole | 90 (25.9%) | |
| Ribociclib plus fulvestrant | 80 (23%) | |
| Disease setting | | 0.48 |
| De novo metastatic | 173 (49.1%) | |
| Recurrent | 174 (50.9%) | |
| Treatment line | | **< 0.001** |
| 1. line | 203 (58.5%) | |
| 2. line | 83 (23.9%) | |
| 3. or more lines | 61 (17.6%) | |
| Treatments prior to CDK4/6 inhibitors | | **0.001** |
| CT | 79 (22.7%) | |
| ET | 128 (37.1%) | |
| Site of metastasis | | **0.033** |
| Bone only | 124 (35.7%) | |
| Liver | 75 (21.6%) | |
| Lung | 137 (39.5%) | |
| CNS | 5 (1.4%) | |
| CDK 4/6 inhibitor dose reduction | | 0.55 |
| Yes | 120 (35.1%) | |
| No | 222 (64.9%) | |

ECOG PS: Eastern Cooperative Oncology Group Performance Status

PR: Progesterone receptor

CT: Chemotherapy

ET: Endocrine therapy

CNS: Central Nervous System

for the three patient groups. For group 2, the presence of liver metastasis was numerically higher than the other two groups, although it was not statistically significant (19%, 24.7% and 18%, respectively; $p=0.44$).

Median PFS (mPFS) for whole group was 18.3 (95% CI,14.3–22.3) months. There was no significant difference in mPFS between age groups ($p=0.75$). mPFS for group 1 was 20.7 months, for group 2 it was 18.2 months, and for group 3 it was 13.4 months (Fig. 1).

The initial treatment response was progression in 11.5% of patients (18 patients in group 1, 19 patients in group 2, and 2 patients in group 3). The objective response rate (ORR) was 62.5%, with 7.9% having a complete response.

The estimated median OS (mOS) was 39.5 (95% CI, 24.9–54.1) months and there was no significant difference between age groups ($p=0.15$) (Fig. 2).

Grade 3–4 AEs were reported in 42.7% for the entire group, and neutropenia was the most common (37.3%). There was no significant difference in terms of grade 3–4 AEs between age groups ($p=0.52$). 3.1% of the patients were permanently discontinued treatment due to AEs. Any unexpected side effects or exitus due to AEs were not reported. No correlation between any grade of AEs and survival was shown.

According to univariate analysis, there was a significant association between mPFS and the presence of liver disease at CDK4/6i initiation ($p=0.008$) (Fig. 3) and receiving systemic therapy for MBC before CDK4/6i treatment ($p=0.001$) (Fig. 4).

According to multivariable analysis, mPFS was only associated with receiving systemic therapy for MBC before CDK4/6i treatment. Patients who did not receive CDKi therapy as first-line had 1.9-fold (1.26–2.77) increase in risk of progression/death ($p=0.002$). Included variables are shown in the Table 2.

When evaluating mPFS separately in the first line and second line according to age-based subgroup; no significant difference in mPFS was demonstrated between age subgroups. However, while survival curves overlapped in patient groups who received treatments prior to CDK4/6is (mPFS were 13.1-14.2-NA months for group 1 and 2 and 3, respectively; $p=0.47$) (Fig. 5), treatment-naive patients for MBC before CDK4/6i treatment exhibited a meaningful difference of numerical benefit (mPFS were 37.3-22-13.4 months for group 1 and 2 and 3, respectively; $p=0.21$) (Fig. 6).

## Discussion

Our study aimed to further reveal the characteristics of the geriatric patient group over 65 years of age, which is relatively underrepresented in prospective RCTs. The fact that the general population is aging and a higher proportion of patients diagnosed with MBC is in the elderly group also increasingly gained importance. The results of our study are remarkable in terms of reflecting the heterogeneous treatment group and real-life data.

Regarding the grouping of patients according to their ages in our cohort, primarily, we accepted patients aged 65 and over as elderly in accordance with the global definition. However, this definition is not based on conclusive medical or biological evidence and is open to scientific debate. Based on clinical endpoints related to cognitive and functional abilities, some studies have evaluated differences by changing the cut-off age of elderly individuals to 70 or 75 [9–11]. Based on

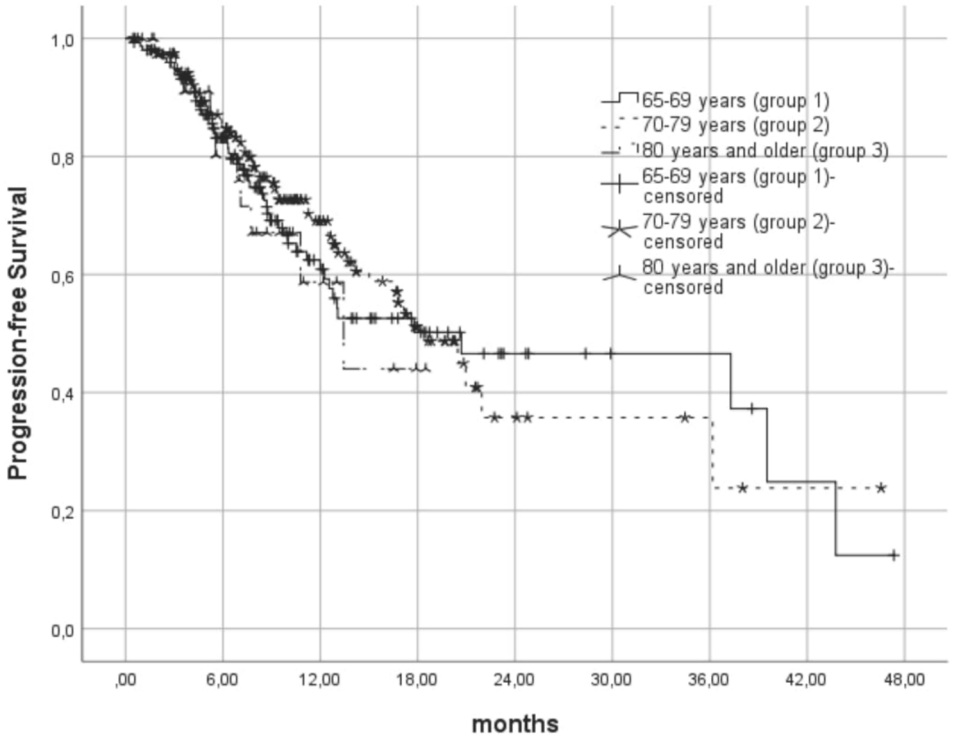


**Fig. 1** mPFS for age subgroups

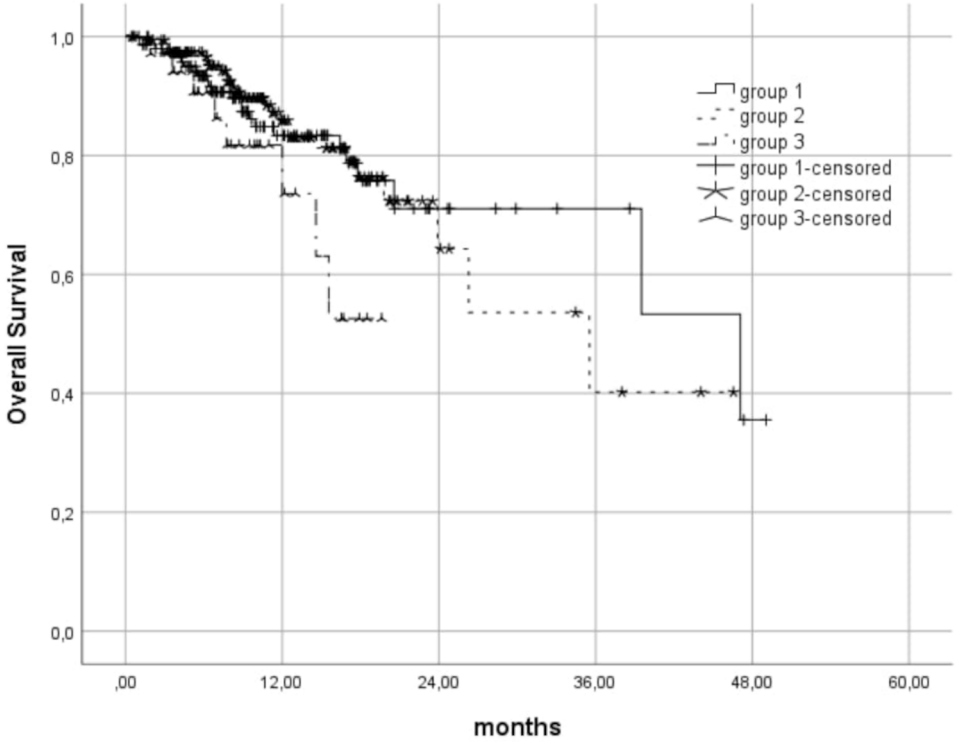


**Fig. 2** mOS for age subgroups

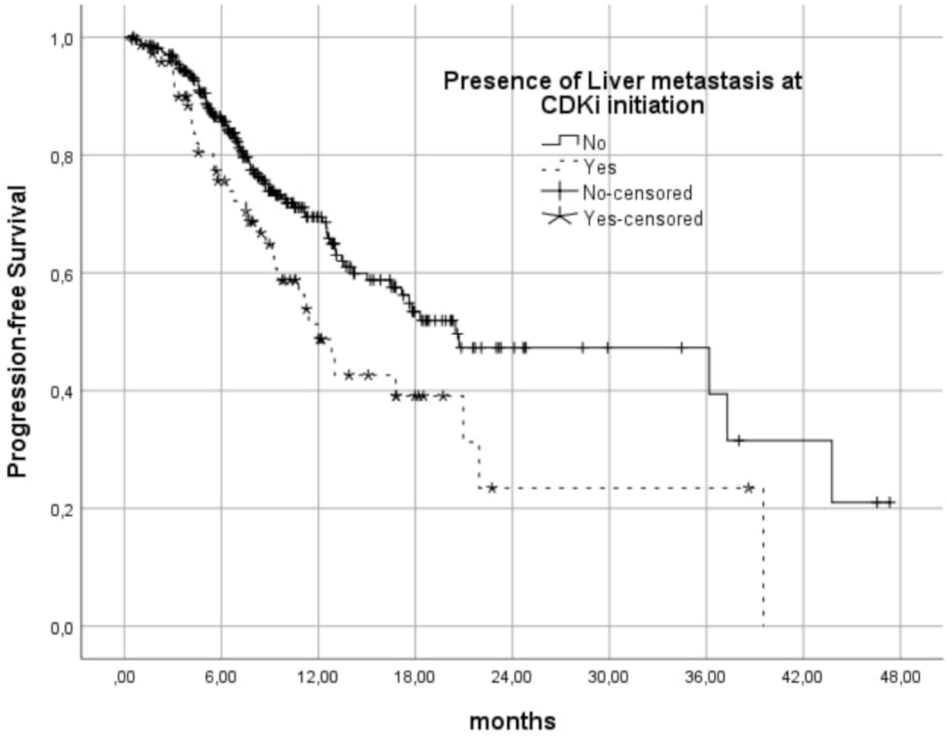


**Fig. 3** Association between the presence of liver metastasis at CDK4/6i initiation and mPFS

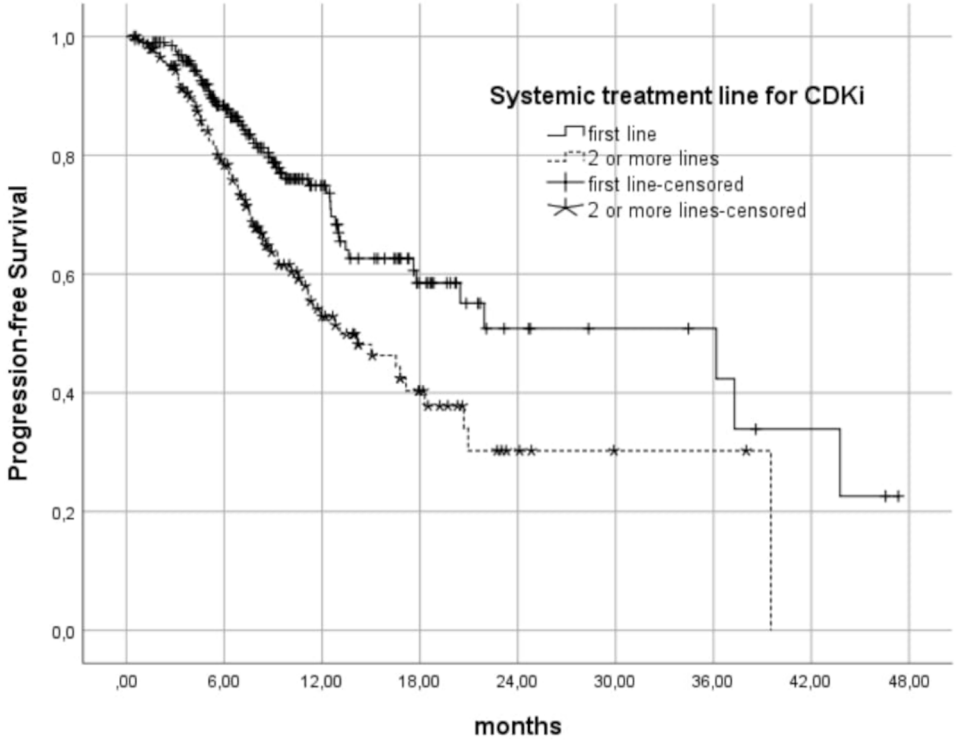


**Fig. 4** Association between receiving treatment for MBC before CDK4/6i and mPFS

**Table 2** The multivariate analysis of variables for progression-free survival

| Variables | | HR (95% CI) | *p* value |
|---|---|---|---|
| Age | ≤ 70 vs. > 70 | 0.91 (0.62–1.34) | 0.64 |
| Comorbidity | Yes vs. no | 0.76 (0.50–1.17) | 0.22 |
| Ecog ps | 0–1 vs. 2 | 1.5 (0.91–2.60) | 0.16 |
| Metastases site | Bone only vs. visseral | 1.2 (0.76–1.88) | 0.44 |
| Liver metastasis | Yes vs. no | 1.56 (0.97–2.25) | 0.61 |
| CDK4/6 treatment line | Subsequent vs. In first line | **1.87 (1.26–2.77)** | **0.002** |
| Grade ≥ 3 adverse events | Yes vs. no | 0.92 (0.62–1.37) | 0.70 |

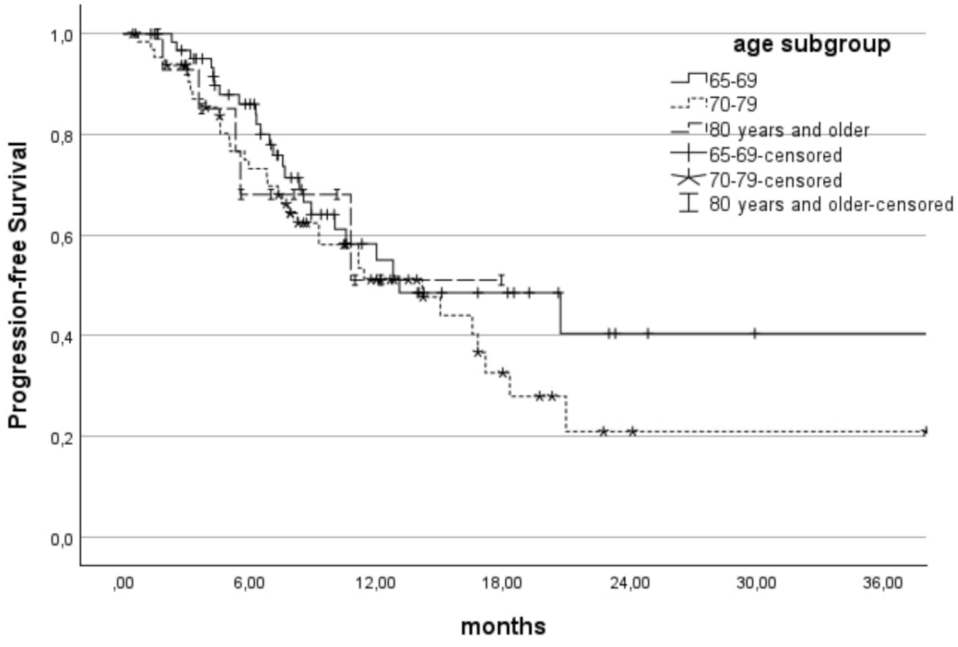


**Fig. 5** mPFS in patient age-groups who received treatments prior to CDK4/6is

studies that suggest changing the definition of elderly, in a recent study investigating real-world experience in patients with HR+/HER2- MBC receiving CDK4/6is, an age cut-off of 70 years was accepted as the definition of elderly [12, 13]. A recent study evaluating the pharmacokinetic variability of palbociclib in patients with HR+/HER2- MBC receiving palbociclib as first- or second-line therapy in combination with aromatase inhibitors or fulvestrant reported that percentage deviation from the median Ctrough (minimum plasma concentrations) of palbociclib was higher for the patients older than 65 years compared with patients under 65 years of age [14]. This study also suggests the necessity of evaluating the comparative pharmacokinetics of patients over 65 years of age in patients receiving CDK4/6i treatment.

On the other hand, according to the subsequently reported outcomes of the RCTs and their retrospective pooled analysis, the efficacy data for the combination of CDK4/6i and ET in the elderly group are independent of age [7, 15–17]. An age-specific pooled analysis of the Monarch studies comparing young and old showed no differences in mPFS between age groups [5, 16]. Another pharmacology-based study reported that systemic exposure to CDK4/6is may be affected by pharmacogenetic processes rather than age, meaning that efficacy and safety may vary depending on under/overexposure status that develops via enzymatic pathways [18]. Therefore, the general similarity of the outcomes obtained with CDK4/6i treatments for the elderly group both within and when compared to younger patients may be explained by this finding.

In our study, consistent with the literature, it was shown that real-life survival data in elderly patients did not show a statistically significant difference between age groups. Median PFS was numerically unfavorable in group 3 over the age of 80, but it was not statistically significant. Additional medical conditions such as increased frailty and comorbidities with aging or the inevitable higher mortality rates in older population and the assessment of death as progression may contribute to this result.

This study demonstrated favorable overall response rates (ORRs) compared to a similar retrospective study

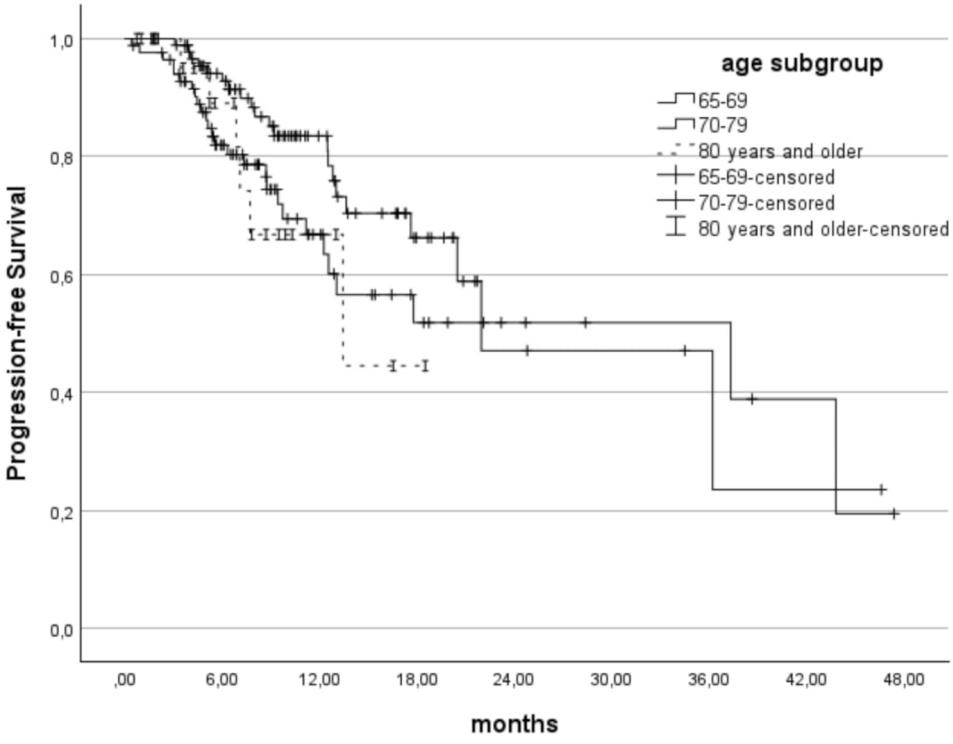


**Fig. 6** mPFS in patients untreated for MBC before CDK4/6i treatment according to age-groups

by Pla et al. [19]. Higher proportion of patients over the age of 70 were present in our study. However due to their retrospective nature, it is not possible to compare two studies.

The drug dose reduction rate was generally similar to PALOMA 2 and 3 trials in our study [20, 21]. In the 1st and 2nd groups, dose reduction was 31% and 34%, while in the 3rd group, dose reduction was performed in 50% of the patients. A recent real-world study investigating the tolerability of palbociclib in older women (≥ 70years) reported grade 3–4 adverse event rates and dose reduction rates approximately similar to ours [22]. Nevertheless, the permanent discontinuation rate in our study was generally lower than even literature data on the general population [23] and also elderly patient group [7, 19, 22, 24, 25]. These findings may be related to possible underreporting in healthcare provider records.

In line with published data, drug dose reduction did not compromise survival in the elderly patient population either [8, 19, 26]. However, it is unclear whether the higher rate of drug reduction required in the oldest age group is a factor contributing to inferior survival. Due to its retrospective nature, the study cannot reveal whether the dose reductions were consistent with published data from randomized trials, particularly for the management of neutropenia. Another limitation is the potential bias associated with healthcare provider records, so results should be interpreted with caution.

There was no difference in the presence of grade 3–4 side effects between age groups ($p=0.60$), suggesting that CDK4/6i tolerability is appropriate for the elderly and the oldest age groups. The presence of accompanying comorbidities was significantly higher in Groups 2 and 3 than in Group 1 (76%, 80% and 66%, respectively, $p=0.022$). The study did not reveal the extent to which comorbidities were related to patient survival or the possible effect of polypharmacy on reducing drug efficacy. Another limitation of our study is that sensitivity analysis (i.e. propensity score matching) could not be performed in our study.

A noteworthy finding was that when CDK4/6i treatment was given as the first line, a significant difference in the numerical benefit regarding survival was observed between age groups, with a marked tendency for decreasing benefit with age. Although more pronounced for group 1, this trend in benefit suggests that CDK4/6i therapy is more beneficial as first-line therapy for patients of all age groups and is also tolerable and safe.

As classical knowledge, the presence of liver disease at the start of CDK 4/6i treatment and the administration of CDK4/6i as the first line treatment for MBC were found to be associated with worse survival. We also reached the same conclusion in our study. On the

other hand, we were able to report mPFS and mOS as survival outcomes of our retrospective study and investigated the parameters affecting mPFS. It should also be taken into account that mPFS is not the most commonly adopted primary endpoint when evaluating anticancer drugs [27].

Unfortunately, due to the retrospective design, some important features such as G8 score, Charlson score and quality of life data, which are necessary for the evaluation of the geriatric population, could not be defined, especially in people aged 70 years and over with increased frailty. A comprehensive literature review reported that overall HR-QoL was generally preserved with CDK4/6is [28]. A retrospective observational study included 19 patients ≥ 75 years old diagnosed with HR+/HER2 MBC, with poor performance status and significant comorbidities, and treated with CDK4/6 is [29]. The study Comprehensive Geriatric Assessment scales were performed. A high risk of frailty and frequent but relatively low-grade drug-related toxicity were reported. Studies investigating QOL in elderly patients in a larger cohort using 3 different CDK4/6is agents with different safety profiles are necessary to consolidate clinical practice.

In the near future, the search for CDK4/6is resistance mechanisms and response predictive biomarkers continues. Studies investigating biomarker-based treatment selection regarding treatment sequencing have been reported [30]. Liquid biopsy-guided strategies for continuation beyond progression of CDK4/6is has been investigated [31]. Determining the ideal treatment line of CDK4/6 and its combination partner in the elderly group using ctDNA analysis, a non-invasive method, is an important area of research.

## Conclusion

Among the HR+/HER2- MBC patient group, proportion of elderly patients is expected to meaningfully increase. In parallel, our knowledge about elderly patients receiving CDK 4/6i for the treatment of HR+/HER2- MBC is accumulating. In order to contribute to the literature we presented efficacy and safety data in three different age subgroups in elderly patients in our retrospective study. As a result of this study, combination therapy with palbociclib or ribociclib with an endocrine therapy partner can be assumed to have practically similar efficacy and be safe among older patient subgroups diagnosed with HR+/HER2- MBC. More data are required to elucidate the optimal sequence of CDK4/6i combination therapy, dose modification and AEs management, and improvement in quality of life, particularly for the frail patient group aged 70 years and older, which mostly underrepresent in studies.

**Author contributions**

Conception and design: Professor Dr. Mehmet Ali Nahit Sendur, Dr. Mutlu Hizal and Dr. Seda Kahraman; Development of methodology, analysis and interpretation of data, and writing of the article: Dr. Seda Kahraman and Professor Dr. Mehmet Ali Nahit Sendur; Data acquisition, Manuscript writing : Dr. Seda Kahraman, Professor Dr. Mehmet Ali Nahit Sendur, Dr. Mutlu Hizal, Burcin Cakan Demirel, Deniz Can Guven, Ozge Gumusay, Basak Oyan Uluc, Ertugrul Bayram, Burcu Gulbagci, Alper Yasar, Sena Ece Davarci, Eda Eylemer Mocan, Omer Acar, Deniz Isik, Esra Aydin, Yusuf Karakas, Melike Ozcelik, Murat Keser, Sadi Kerem Okutur, Onder Eren, Serkan Menekse, Dincer Aydin, Funda Yilmaz, Ozlem Dogan, Gulhan Ozkanli, Hakan Yucel, Veli Sunar, Musa Baris Aykan, Ozlem Ozdemir, Berna Bozkurt Duman, Merve Keskinkilic, Teoman Sakalar, Muge Karaoglanoglu, Asude Aksoy, Muhammed Muhiddin Er, Nazim Serdar Turhal, Nurhan Onal Kalkan; Final approval of manuscript: Dr. Seda Kahraman. All authors revised the manuscript critically for important intellectual content and approved the revised version to be published.

**Funding**

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

**Data availability**

No datasets were generated or analysed during the current study.

## Declarations

**Ethics approval and consent to participate**

The study protocol was approved by the Clinical Research Ethics Committee chaired by the Ankara City Hospital Institutional Review Board. Informed consent was waived by our institutional review board because no experimental procedures were performed.
The preparation of the article was followed in accordance with the STROBE guidelines. We conducted this study according to the Declaration of Helsinki.

**Consent for publication**

Not Applicable.

**Competing interests**

The authors declare no competing interests.

**Author details**

[1]Ankara Bilkent City Hospital, Department Of Medical Oncology, Ankara Yildirim Beyazit University, Ankara 06800, Turkey
[2]Department Of Medical Oncology, Pamukkale University Hospital, Denizli, Turkey
[3]Department of Medical Oncology, Hacettepe University Cancer Institute, Ankara, Turkey
[4]School of Medicine, Department of Medical Oncology, Acibadem University, Istanbul, Turkey
[5]Department Of Medical Oncology, Cukurova University Faculty of Medicine, Adana, Turkey
[6]Department of Medical Oncology, Sakarya University School of Medicine, Sakarya, Turkey
[7]Department Of Medical Oncology, Marmara University Pendik Research and Application Hospital, Istanbul, Turkey
[8]Department of Medical Oncology, Afyonkarahisar Health Sciences University, Afyonkarahisar, Turkey
[9]Department Of Medical Oncology, Ankara University Faculty of Medicine, Ankara, Turkey
[10]Department Of Medical Oncology, Manisa Celal Bayar University Hospital, Manisa, Turkey
[11]Department Of Medical Oncology, Kocaeli Medical Park Hospital, Kocaeli, Turkey
[12]Department Of Medical Oncology, Recep Tayyip Erdoğan University Training and Research Hospital, Rize, Turkey
[13]Department Of Medical Oncology, Acıbadem Bodrum Hospital, Mugla, Turkey
[14]Department Of Medical Oncology, Umraniye Training and Research Hospital, Istanbul, Turkey
[15]Department Of Medical Oncology, Tepecik Training and Research Hospital, Izmir, Turkey

[16]Department Of Medical Oncology, Istanbul Arel University, Bahcelievler Memorial Hospital, Istanbul, Turkey
[17]Department Of Medical Oncology, Selcuk University Medical Faculty Hospital, Konya, Turkey
[18]Department Of Medical Oncology, Manisa City Hospital, Manisa, Turkey
[19]Department Of Medical Oncology, Kocaeli Derince Training and Research Hospital, Kocaeli, Turkey
[20]Department Of Medical Oncology, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Ankara, Turkey
[21]Department Of Medical Oncology, Ankara Etlik City Hospital, Ankara, Turkey
[22]Department Of Medical Oncology, Canakkale Onsekiz Mart University Research And Practice Hospital, Canakkale, Turkey
[23]Faculty of Medicine, Department of Medical Oncology, Gaziantep University, Gaziantep, Turkey
[24]Department Of Medical Oncology, Aydin Ataturk State Hospital, Aydin, Turkey
[25]Department Of Medical Oncology, Gulhane Training and Research Hospital, Ankara, Turkey
[26]Department Of Medical Oncology, Izmir Bozyaka Training and Research Hospital, Izmir, Turkey
[27]Department Of Medical Oncology, Adana City Training and Research Hospital, Adana, Turkey
[28]Department Of Medical Oncology, Dokuz Eylül University Research and Application Hospital, Izmir, Turkey
[29]Department Of Medical Oncology, Kahramanmaras Necip Fazil City Hospital, Kahramanmaras, Turkey
[30]Department Of Medical Oncology, Mersin City Hospital, Mersin, Turkey
[31]Department Of Medical Oncology, Ordu State Hospital, Ordu, Turkey
[32]Department Of Medical Oncology, Elazig Fethi Sekin City Hospital, Elazig, Turkey
[33]Department Of Medical Oncology, Necmettin Erbakan University Meram Medical Faculty Hospital, Konya, Turkey
[34]Department Of Medical Oncology, Anadolu Medical Center, Gebze, Turkey
[35]Department Of Medical Oncology, Van Yüzüncü Yıl University Dursun Odabas Hospital, Van, Turkey

Received: 3 August 2024 / Accepted: 17 December 2024
Published online: 30 December 2024

**References**

1. Rugo HS, et al. Effect of palbociclib plus endocrine therapy on time to chemotherapy across subgroups of patients with hormone receptor–positive/human epidermal growth factor receptor 2–negative advanced breast cancer: Post hoc analyses from PALOMA-2 and PALOMA-3. Breast. 2022;66:324–31.
2. Hortobagyi GN, et al. Ribociclib as First-Line therapy for HR-Positive, advanced breast Cancer. N Engl J Med. 2016;375(18):1738–48.
3. Goetz MP, et al. MONARCH 3: Abemaciclib as initial therapy for advanced breast Cancer. J Clin Oncol. 2017;35(32):3638–46.
4. Giuliano M, et al. Endocrine treatment versus chemotherapy in postmenopausal women with hormone receptor-positive, HER2-negative, metastatic breast cancer: a systematic review and network meta-analysis. Lancet Oncol. 2019;20(10):1360–9.
5. Petrelli F, et al. The role of CDK4/6 inhibitors in older and younger patients with breast cancer: a systematic review and meta-analysis. Breast. 2023;71:138–42.
6. Freedman RA, Tolaney SM. Efficacy and safety in older patient subsets in studies of endocrine monotherapy versus combination therapy in patients with HR+/HER2- advanced breast cancer: a review. Breast Cancer Res Treat. 2018;167(3):607–14.
7. Howie LJ, et al. Outcomes of older women with hormone Receptor-Positive, human epidermal growth factor receptor-negative metastatic breast Cancer treated with a CDK4/6 inhibitor and an aromatase inhibitor: an FDA pooled analysis. J Clin Oncol. 2019;37(36):3475–83.
8. Rugo HS, et al. Palbociclib plus endocrine therapy in older women with HR+/HER2- advanced breast cancer: a pooled analysis of randomised PALOMA clinical studies. Eur J Cancer. 2018;101:123–33.
9. Jacobs JM, et al. Changing profile of health and function from age 70 to 85 years. Gerontology. 2012;58(4):313–21.
10. Singh S, Bajorek B. Defining 'elderly' in clinical practice guidelines for pharmacotherapy. Pharm Pract (Granada). 2014;12(4):489.
11. Ouchi Y, et al. Redefining the elderly as aged 75 years and older: proposal from the Joint Committee of Japan Gerontological Society and the Japan Geriatrics Society. Geriatr Gerontol Int. 2017;17(7):1045–7.
12. O'Connor TN et al. Real-world experience among Elderly metastatic breast Cancer patients treated with CDK4/6 inhibitor-based therapy. Cancers (Basel), 2024. 16(9).
13. Biganzoli L, et al. Updated recommendations regarding the management of older patients with breast cancer: a joint paper from the European Society of breast Cancer specialists (EUSOMA) and the International Society of Geriatric Oncology (SIOG). Lancet Oncol. 2021;22(7):e327–40.
14. Peruzzi E et al. Exploring pharmacokinetic variability of palbociclib in HR+/HER2- metastatic breast cancer: a focus on age, renal function, and drug–gene interactions. Front Pharmacol, 2024. 15.
15. Giraudo A, et al. The use of cyclin-dependent kinase 4/6 inhibitors in Elderly breast Cancer patients. Volume 16. What Do We Know? Cancers (Basel); 2024. 10.
16. Goetz MP, et al. Safety and efficacy of abemaciclib plus endocrine therapy in older patients with hormone receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer: an age-specific subgroup analysis of MONARCH 2 and 3 trials. Breast Cancer Res Treat. 2021;186(2):417–28.
17. Muller C, et al. CDK4/6 inhibitors in Advanced HR+/HER2 - breast Cancer: a Multicenter Real-World Data Analysis. Breast Care (Basel). 2023;18(1):31–41.
18. Roncato R, et al. An Integrated Pharmacological Counselling Approach to Guide decision-making in the treatment with CDK4/6 inhibitors for metastatic breast Cancer. Front Pharmacol. 2022;13:897951.
19. Pla H, et al. Elderly patients with hormone receptor-positive HER2-negative metastatic breast cancer treated with CDK4/6 inhibitors in a multicentre cohort. Clin Transl Oncol. 2024;26(7):1748–58.
20. Finn RS, et al. Palbociclib and Letrozole in Advanced breast Cancer. N Engl J Med. 2016;375(20):1925–36.
21. Cristofanilli M, et al. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. Lancet Oncol. 2016;17(4):425–39.
22. Baltussen JC, et al. Tolerability and effectiveness of palbociclib in older women with metastatic breast cancer. Breast Cancer Res Treat. 2024;206(2):337–46.
23. Mycock K, et al. Real-world treatment patterns and clinical outcomes Associated with Palbociclib Combination Therapy: a multinational, pooled analysis from the Ibrance Real World insights Study. Clin Ther. 2022;44(12):1588–601.
24. Sonke GS, et al. Ribociclib with letrozole vs letrozole alone in elderly patients with hormone receptor-positive, HER2-negative breast cancer in the randomized MONALEESA-2 trial. Breast Cancer Res Treat. 2018;167(3):659–69.
25. Olazagasti C, et al. A deep dive into CDK4/6 inhibitors: evaluating real world toxicities and treatment paradigms in the elderly population. J Oncol Pharm Pract. 2023;29(1):14–21.
26. Clifton K, et al. Progression-free survival (PFS) and toxicities of palbociclib in a geriatric population. Breast Cancer Res Treat. 2019;175(3):667–74.
27. Booth CM, et al. Progression-free survival should not be used as a primary End Point for Registration of Anticancer drugs. J Clin Oncol. 2023;41(32):4968–72.
28. Di Lauro V, et al. Health-related quality of life in breast cancer patients treated with CDK4/6 inhibitors: a systematic review. ESMO Open. 2022;7(6):100629.
29. Sobrini-Morillo P, et al. Real-world experience with CDK4-6 inhibition in the old and oldest old with a diagnosis of breast cancer. Semin Oncol. 2024;51(3–4):95–105.
30. Schettini F, et al. CDK4/6-Inhibitors Versus Chemotherapy in Advanced HR+/HER2-Negative breast Cancer: results and correlative biomarker analyses of the KENDO Randomized Phase II Trial. Oncologist. 2024;29(5):e622–34.

31. Gerratana L, et al. Cyclin-dependent kinase 4/6 inhibitors beyond progression in metastatic breast Cancer: a retrospective real-world biomarker analysis. JCO Precis Oncol. 2023;7:e2200531.

## Publisher's note