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Original Article

Efficacy and Safety of CDK4/6 Inhibitor Therapy in Patients Aged 70 and Older with Metastatic Breast Cancer: A Retrospective Single-Center Analysis

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Keywords: CDK4/6 inhibitor; ECOG performance status; elderly patients; HER2-negative; hormone receptor-positive; metastatic breast cancer; overall survival; progression-free survival.

ABSTRACT

Objective: This study aimed to evaluate the effectiveness and safety of CDK4/6 inhibitor therapy in patients aged ≥70 years diagnosed with hormone receptor-positive (HR+) HER2-negative metastatic breast cancer (MBC). Given the unique challenges faced by older adults due to comorbidities and potential treatment-related toxicities, this study aimed to provide insights into real-world outcomes in this population.

Methods: This retrospective, single-center analysis included 43 patients aged ≥70 years diagnosed with HR+ HER2- MBC who started CDK4/6 inhibitor treatment between May 2020 and December 2022. Data were collected from medical records, including demographics, ECOG performance status, treatment details, and adverse events. Progression-free survival (PFS) and overall survival (OS) were evaluated using Kaplan-Meier analysis, whereas subgroup comparisons were performed using log-rank tests. Cox proportional hazard models were used to identify the factors associated with PFS and OS.

Results: The median age was 76.7 years, and 46.5% of the patients presented with de novo metastasis. CDK4/6 inhibitors were administered as first-line treatment in 41.9% of patients, second-line therapy in 46.5 %, and third-line therapy in 11.6 %. The median PFS was 16.0 months, with patients with ECOG PS 0 or 1 achieving significantly longer PFS (20.0 months) than those with ECOG PS≥2 (5.8 months, $p<0.01$). The median OS was 25.3 months, with better outcomes for ECOG PS 0 or 1 (29.3 months) than for ECOG PS≥2 (15.9 months, $p<0.01$). Dose reductions occurred in 32.6% of patients but did not significantly affect the PFS.

Conclusion: CDK4/6 inhibitors are effective in older adults with HR+ HER2- MBC, particularly those with an ECOG PS of 0 or 1 with manageable toxicities with dose reductions. These findings highlight the importance of assessing ECOG PS when managing treatment in older patients. Dose adjustments were feasible without compromising efficacy, suggesting that personalized treatment can optimize outcomes. Further research with larger cohorts is required to confirm this hypothesis.

INTRODUCTION

Metastatic breast cancer (MBC) continues to pose a significant health challenge, particularly in older women. The likelihood of breast cancer diagnosis increases with age. Patients aged ≥70 years account for a significant proportion of MBC cases.[1] This population often faces unique treatment challenges owing to comorbidities, organ dysfunction, and the possibility of heightened treatment-related toxicity.[2,3]

Inhibitors of cyclin-dependent kinase 4/6 (CDK4/6) have emerged as promising treatment alternatives for hormone receptor-positive (HR+) and HER2-negative (HER2-) MBC. The use of these inhibitors, together with endocrine therapy (ET), has resulted in significant improvements in progression-free survival (PFS) and overall survival (OS).[4-6] For example, a pooled analysis indicated that CDK4/6 inhibitors combined with AI led to a median PFS of 31.1 months in patients aged ≥75 years.[5] This underscores the effectiveness of these inhibitors in prolonging the progression time in older individuals. However, the administration of these treatments to older patients presents challenges. Clinical trials frequently overlook older participants and lack age-specific information regarding efficacy and safety.

[2,3]

Moreover, these patients experience higher rates of adverse events and may require more frequent dose modifications.[5,7] A previous study indicated that almost 90% of patients aged ≥75 years experienced grade 3-4 adverse effects, whereas 73.4% of younger patients experienced similar events.[5] Furthermore, real-world data suggest that older patients are less inclined to be treated with CDK4/6 inhibitor therapy, with usage rates being significantly lower in those aged ≥70 years.

Considering the distinct obstacles and low participation of older patients in clinical studies, we aimed to assess the efficacy and safety of these treatments, focusing mainly on patients aged ≥70 years with MBC. By focusing on this demographic, our study sought to provide insights into the real-world outcomes, treatment tolerability, and potential benefits of CDK4/6 inhibitor therapy in older adult patients. This targeted analysis can help bridge the knowledge gap in managing HR+ HER2 − MBC in older populations. This may guide personalized treatment strategies to optimize the efficacy and quality of life in this vulnerable patient group.

MATERIALS AND METHODS

This single-center study reviewed the efficacy and safety of CDK4/6 inhibitors in elderly patients diagnosed with HR+, HER2 − MBC. We included patients who received CDK4/6 in combination with ET as first-line or subsequent treatment. Eligible participants were aged ≥70 years at treatment initiation and had confirmed HR+ HER2- MBC based on histopathological reports. Patients with other primary malignancies were also excluded from the analyses.

Data Collection

Clinical information, including demographics, coexisting health issues, Eastern Cooperative Oncology Group Performance Status (ECOG PS), past treatments, and laboratory findings, were gathered retrospectively from medical records. Details regarding treatment, including the specific CDK4/6 inhibitor utilized (palbociclib or ribociclib), line of therapy, dosing, and any dose modifications, were also recorded. Adverse events were assessed according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (8). Disease progression and response were evaluated according to the RECIST 1.1 criteria in the radiological assessment reports.[9]

Outcomes

The main objective of this study was PFS, defined as the period from the initiation of CDK4/6 inhibitor therapy until disease progression or death. The secondary objectives encompassed OS, defined as the time from the initiation of treatment to death from any cause, and safety, which focused on the occurrence and severity of treatment-related adverse events. Other outcomes included the frequency of dosage reduction and treatment discontinuation due to adverse effects.

Statistical Analysis

Descriptive statistics were used to summarize patient characteristics, treatment regimens, and adverse events. Kaplan-Meier survival analysis was used to evaluate PFS and OS, and log-rank tests were used to compare survival between subgroups. Cox proportional hazard models were used to determine the factors associated with PFS and OS. Statistical significance was set at $p<0.05$. Variables with p-values of <0.05 in the univariate analysis and factors that may have contributed to survival were included in the multivariate analysis. Statistical analyses were performed using SPSS version 27.0 (IBM Corp., Armonk, NY, USA)

Ethical Considerations

This study complied with the Declaration of Helsinki and adhered to the ethical standards. For this retrospective analysis, ethical approval was obtained from the Institutional Ethical Board of our Hospital (Approval No: 2024/010.99/9/31, Date: 25.10.2024). Owing to the retrospective nature of the study, the requirement for informed consent was waived, and all patient data were anonymized to ensure confidentiality.

RESULTS

Patient Characteristics

A total of 43 patients aged ≥70 years who were diagnosed with HR +/HER2-MBC and initiated treatment with CDK4/6 inhibitors between May 2020 and December 2022 were included in the study. The mean age was 76.7 years (70-92). Among these patients, ten patients (23.3%) had ECOG PS 0, 22 (52.4%) had ECOG PS 1, and 10 (23.3%) had ECOG PS ≥ 2. Furthermore, 46.5% of the study population was diagnosed with de novo metastasis.

Among the total cohort, 18 patients (41.9%) received CDK4/6 inhibitor treatment as first-line therapy, 20 (46.5%) initiated CDK4/6 inhibitors as second-line therapy, and 5 (11.6%) received them as third-line therapy. Palbociclib and ribociclib were administered to 62.8% and 37.2% of patients, respectively. Fulvestrant was administered more frequently with CDK4/6 inhibitors (55.8 %), whereas letrozole was administered in 44.2% of cases. Regarding metastatic site involvement, bone metastasis was the most common metastatic site, with 32 (74.4%) patients having bone metastasis and 27 (62.8%) having visceral metastasis (Table 1).

Efficacy

During the analysis, 65.1% of patients experienced disease progression while receiving CDK4/6 inhibitor treatment. Regarding treatment responses, partial response was the most frequent radiological response (65.1%), while 5 (11.6%) had stable disease and 10 (23.3%) had progressive disease. The PFS for the initial line of treatment was 14.7

Table 3. Baseline characteristics of patients aged 70 and above treated with CDK4/6 inhibitors (N=43)

Category	N=43 (%)
Age	
Median (range)	75 (70-92)
ECOG PS	
0	10 (23.3)
1	22 (51.2)
2	10 (23.3)
Line of Treatment	
1st Line	18 (41.9)
2nd Line and Beyond	25 (58.1)
CDK 4/6 Inhibitor	
Palbociclib	27 (62.8)
Ribociclib	16 (37.2)
Hormone Therapy	
Letrozole	19 (44.2)
Fulvestrant	24 (55.8)
Metastasis at Diagnosis	
Yes	20 (46.5)
No	23 (53.5)
Estrogen Receptor	
<50	6 (14)
≥50	37 (86)
Metastasis Location	
Bone	32 (74.4)
Lung	15 (34.9)
Liver	8 (18.6)
Visceral Metastases	
Yes	27 (62.8)
Bone Lesions Only	
Yes	8 (18.6)

ECOG PS: Eastern Cooperative Oncology Group Performance Status; CDK 4/6: Cyclin-Dependent Kinase 4/6.

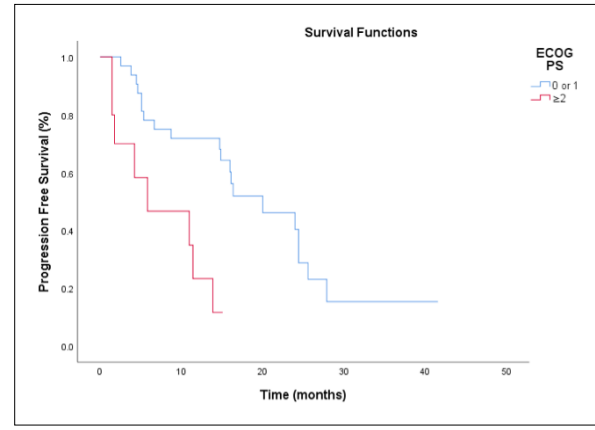

Figure 1. Kaplan-Meier curve for progression-free survival stratified by ECOG PS.
ECOG PS, Eastern Cooperative Oncology Group Performance Status.

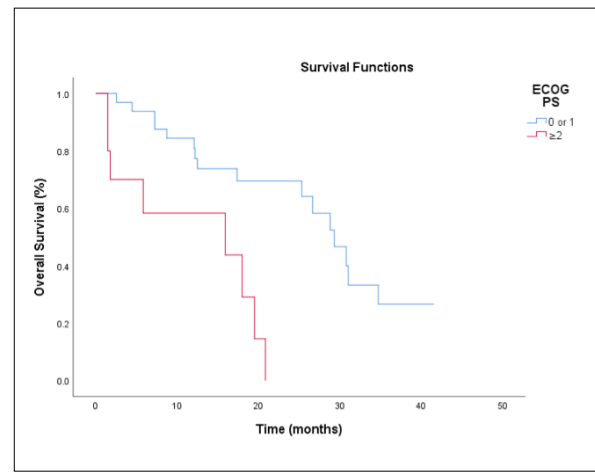

Figure 2. Kaplan-Meier Curve for Overall Survival Stratified by ECOG PS.
ECOG PS, Eastern Cooperative Oncology Group Performance Status.

months (95% CI, 1.0–28.4), whereas for subsequent lines of treatment, it was 16.1 months (95% CI, 13.8–18.4). Among the whole cohort, 24 (55.8%) patients have died, and the median OS was 25.3 months (95% CI, 15.1-35.6).

In our analysis, ECOG PS significantly affected PFS (20.0 vs 5.8 months; HR, 4.230; 95% CI, 1.670–10.717; p<0.01) (Fig. 1). Additionally, the presence of visceral metastases was linked to reduced PFS (11.4 vs. 20.0 months; HR, 0.373; 95% CI: 0.156–0.891; p=0.026); The type of CDK4/6 inhibitor used did not have a notable effect on PFS (Hazard Ratio [HR], 0.763; 95% CI, 0.344–1.692; p=0.505). Similarly, the treatment line in which the CDK4/6 inhibitor was administered did not significantly affect PFS (HR, 0.715; 95% CI, 0.320–1.595; p=0.412).

For OS, ECOG PS significantly affected OS (29.3 vs. 15.9 months; HR, 4.563; 95% CI, 1.742–11.951; p<0.01) (Fig. 2).

Table 2. Incidence of grade 2–4 toxicities in women aged 70+ receiving CDK4/6 inhibitors

Toxicity Type	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
Neutropenia	11.6%	51.2%	4.7%
Thrombocytopenia	2.3%	16.3%	—
Anemia	23.3%	9.3%	—
Liver Toxicity	—	7.0%	—

In the multivariate analysis, ECOG PS was identified as a significant predictor of PFS (HR, 4.64; 95% CI, 1.75–12.31; p<0.01), while the presence of visceral metastases (HR, 0.48; 95% CI, 0.19–1.21; p=0.12) and dose reductions (HR, 1.51; 95% CI, 0.61- 3.77; p= 0.38) were not found to be significant. Multivariate analysis also showed that ECOG PS was a significant predictor for OS (HR, 4.68; 95% CI, 1.69-12.9; p<0.01) while the presence of visceral metastases (HR, 0.39; 95% CI, 0.24–1.74; p=0.39) and dose reductions (HR, 0.81; 95% CI, 0.32-2.01; p=0.66) were not found to be significant.

The presence of visceral metastases was not linked to OS (HR, 0.54; 95% CI, 0.21-1.36; p=0.19). The type of CDK 4/6 inhibitor used did not have a notable effect on OS (HR, 0.66; 95% CI, 0.31-1.41; p=0.28). The treatment line in which the CDK4/6 inhibitor was administered did not significantly affect OS (HR, 0.9; 95% CI, 0.45-1.78; p=0.75).

Grade 3 toxicity was observed in 60.5% of the patients. Neutropenia was observed in 11.6%, 51.2%, and 4.7% of patients with grade 2, 3, and 4 neutropenia, respectively. Thrombocytopenia occurred less frequently, with 2.3% and 16.3% of patients experiencing grade 2 and grade 3 thrombocytopenia, respectively. Anemia was noted at grade 2 in 23.3% of patients and grade 3 in 9.3%. Additionally, grade 2 and 3 liver toxicity were recorded in three patients (7%) (Table 2).

Of the 43 patients, 14 (32.6%) had their doses reduced. Two patients (4%) discontinued treatment because of toxicity. Although patients with dose reduction had higher PFS, it was insignificant in univariate analysis (24.4 vs. 14.8 months; HR, 1.132; 95% CI, 0.516–2.484; p=0.757) (Fig. 3). Dose reductions also did not have significance on OS (26.6 vs. 28.8 months, HR 0.56; 95% CI, 0.32-1.87; p=0.56).

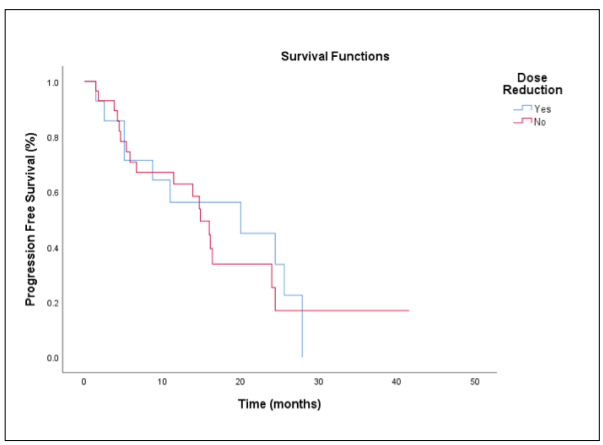

Figure 3. Kaplan-Meier curve for Progression-Free Survival stratified by dose reduction.

DISCUSSION

The PFS and OS analysis in our study emphasized the critical role of ECOG PS in determining treatment outcomes in patients aged ≥70 years with MBC receiving CDK4/6 inhibitors. A significant difference in median PFS was and OS observed between patients with ECOG PS of 0 or 1 and those with ECOG PS of 2 or higher. Specifically, patients with an ECOG PS of 0 or 1 achieved a median PFS of 20.0 months (95% CI, 10.2–29.8), compared with only 5.8 months (95% CI, 0.1–15.2) for those with an ECOG PS of 2 or more (p<0.01). This stark contrast underscores the profound influence of baseline ECOG PS on treatment efficacy, aligning with existing literature that associates poorer ECOG PS with significantly worse PFS (p<0.01) and survival outcomes (HR, 2.3; 95% CI, 1.37–3.79) in multivariable Cox models.[10] In the MONALEESA-3 trial, PFS was higher than that in our study; however, it is important to note that our study cohort included a higher proportion of patients with visceral metastases (53.5% vs. 40% for liver and lung metastases, respectively).[11]

The findings from pivotal trials, such as MONALEESA and PALOMA, support the efficacy of these treatments in HR+ and HER2 − MBC. However, these trials predominantly included patients with an ECOG PS of 0 or 1 and a relatively small number of patients aged ≥65 years, reflecting a healthier cohort. For instance, in the PALOMA-2 trial, only a small subset of participants had ECOG PS 2. This limited representation raises questions regarding the generalizability of the results to more debilitated populations. The efficacy demonstrated in patients with ECOG PS 0 or 1 and relatively young cohort contrast sharply with the outcomes for those with poorer performance statuses, highlighting the need for more inclusive research.[12,13]

Age is another factor that influences treatment outcomes. A comprehensive analysis of studies revealed a statistically significant impact of CDK4/6 inhibitors in younger and older patient groups. Specifically, three studies provided findings for individuals aged <65 and ≥65 years. A statistically significant decrease in the likelihood of death was noted in both subgroups, with HR of 0.80 (95% CI, 0.67–0.95, p=0.01) and 0.71 (95% CI, 0.53–0.95, p=0.003) for patients under 65 years and those 65 years and older, respectively. The cumulative analysis confirmed this benefit, with an HR of 0.77 (95% CI, 0.66–0.88, p<0.001). Notably, there was no significant difference between the subgroups (p=0.49). This indicates that CDK4/6-inhibitor–based therapies are effective in reducing mortality risk for both age groups, producing a 20% and a 29% decrease in the likelihood of death for patients under 65 years and those aged 65 years and above, respectively.[11,14-16]

Regarding safety, our study findings on the use of CDK 4/6 inhibitors in elderly patients revealed significant insights into the toxicity profile of these treatments. Grade 3 toxicity was observed in 60.5% of patients, with neutropenia being a notable adverse event, occurring in 11.6%, 51.2%, and 4.7% of patients with grade 2, 3, and 4 neutropenia,

respectively. Thrombocytopenia and anemia were less frequent but still present, with grade 3 thrombocytopenia and grade 3 anemia in 16.3% and 9.3% of patients, respectively. These findings align with the existing literature, which highlights the increased incidence of adverse events in older populations treated with CDK 4/6 inhibitors compared to younger populations. For instance, studies have shown that while CDK 4/6 inhibitors improve PFS in elderly patients, they also lead to higher rates of grade 3 or higher toxicities, necessitating dose adjustments.[17-19] The literature suggests that despite these toxicities, CDK 4/6 inhibitors are generally well tolerated, and their integration into treatment regimens does not significantly impact the quality of life of elderly patients.[18-20] However, the need for personalized treatment strategies, such as starting with endocrine therapy alone and introducing CDK 4/6 inhibitors upon disease progression, is emphasized to balance efficacy and adverse effects.[19,21] This approach is particularly important given the underrepresentation of older adults in clinical trials, which often leads to extrapolation from younger cohorts.[17,22] Overall, while CDK 4/6 inhibitors present a favorable benefit-risk profile, careful management and further research are necessary to optimize treatment strategies for the elderly population.[18,19,21]

In our study, 32.6% of patients experienced dose reduction due to adverse events. Significantly, these dose reductions did not negatively affect median PFS or OS, suggesting that dose adjustments can be made to manage toxicity without compromising efficacy. This aligns with the findings of other studies, which have reported that dose modifications are often necessary in elderly patients but do not adversely affect treatment outcomes. The ability to adjust doses provides a flexible treatment approach, ensuring that older and more vulnerable patients can benefit from CDK4/6 inhibitors while minimizing toxicity.[23-25]

Despite these insights, a notable gap remains in the evidence regarding CDK4/6 inhibitor use in patients aged ≥70 years, particularly in those with an ECOG PS of 2. Given that older patients are more likely to have a higher ECOG status, understanding the safety and efficacy of this subgroup is essential for improving treatment outcomes. Comprehensive studies on this population are needed to refine treatment strategies and optimize outcomes for older and frail patients.

Conclusion

In conclusion, our findings reaffirm that ECOG performance status is a strong prognostic factor, with patients exhibiting better functional status achieving significantly improved outcomes. Furthermore, dose reductions did not negatively impact treatment efficacy, reinforcing the feasibility of CDK4/6 inhibitors as a viable treatment option despite advanced age.

This study had several limitations. First, its retrospective, single-center design may limit the generalizability of the findings. Second, the sample size was relatively small, which may have affected the statistical power of the subgroup analyses. Third, the study did not assess quality of life outcomes, which are crucial considerations when treating older patients with cancer. Future studies with larger cohorts and prospective designs should further evaluate the impact of CDK4/6 inhibitors on elderly populations.

Ethics Committee Approval

The study was approved by the Kartal Dr. Lütfi Kırdar City Hospital Ethics Committee (Date: 25.10.2024, Decision No: 2024/010.99/9/31).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: O.K.; Design: O.K.; Supervision: D.I.; Data collection &/or processing: O.K.; Analysis and/or interpretation: O.K.; Literature search: D.I.; Writing: O.K.; Critical review: D.I.

Conflict of Interest

None declared.

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70 Yaş ve Üzeri Metastatik Meme Kanseri Hastalarında CDK4/6 İnhibitör Tedavisinin Etkinliği ve Güvenliği

Amaç: Bu çalışma, 70 yaş ve üzeri hormon reseptör pozitif (HR+), HER2-negatif metastatik meme kanserli (MBC) hastalarda CDK4/6 inhibitör tedavisinin etkinliğini ve güvenliğini değerlendirmeyi amaçlamaktadır. Yaşlı hastalarda komorbiditeler ve tedaviye bağlı toksisiteler nedeniyle karşılaşılan özel zorluklar dikkate alındığında, bu araştırma, gerçek dünya verileri üzerinden bu populasyona yönelik bilgi sağlamayı hedeflemektedir.

Gereç ve Yöntem: Retrospektif, tek merkezli bir analizde, Mayıs 2020 ile Aralık 2022 tarihleri arasında HR+ HER2- MBC tanısı konulmuş ve CDK4/6 inhibitör tedavisine başlayan 70 yaş ve üzeri 43 hasta dahil edilmiştir. Elektronik tıbbi kayıtlardan elde edilen veriler demografik bilgiler, ECOG performans durumu (PS), tedavi detayları ve yan etkileri içermektedir. Progressyonsuz sağkalım (PFS) ve genel sağkalım (OS), Kaplan-Meier analizi ile değerlendirilmiş ve alt grup karşılaştırmaları log-rank testleri ile yapılmıştır. PFS ve OS ile ilişkili faktörleri belirlemek için Cox orantılı tehlike modelleri kullanılmıştır.

Bulgular: Ortanca yaş 76.7 yıl olup, hastaların %46.5'i de novo metastaz ile başvurmuştur. CDK4/6 inhibitörleri, hastaların %41.9'una ilk basamak 46.5%'una ikinci basamak olarak ve %11.6'sına da üçüncü basamak olarak verilmiştir. Tüm kohortta ortanca PFS 16.0 ay olmuştur. ECOG PS 0 veya 1 olan hastalar, ECOG PS≥2 olanlara göre anlamlı şekilde daha uzun PFS (20.0 ay) elde etmiştir (5.8 ay, p<0.01). Ortanca OS, ECOG PS 0 veya 1 olanlar için 29.3 ay, ECOG PS ≥2 olanlar için 15.9 ay olmuş ve fark anlamlı bulunmuştur (p<0.01). Toksisite nedeniyle doz azaltımı %32.6 oranında gözlemlenmiş ancak PFS'yi anlamlı derecede etkilememiştir.

Sonuç: CDK4/6 inhibitörleri, HR+ HER2- MBC'li yaşlı hastalarda, özellikle ECOG PS 0 veya 1 olanlarda kontrol edilebilir yan etkili profili ile etkinlik göstermiştir. Bulgular, yaşlı hastalarda tedavi yönetiminde ECOG PS'nin değerlendirilmesinin önemini vurgulamaktadır. Doz ayarlamalarının etkinliği bozmadan uygulanabileceği, kişiselleştirilmiş tedavi ile sonuçların optimize edilebileceğini göstermektedir. Daha geniş kohortlarda daha fazla araştırmaya ihtiyaç vardır.

Anahtar Sözcükler: CDK4/6 inhibitörleri; ECOG performans durumu; genel sağkalım; HER2-negatif; hormon reseptör pozitif; metastatik meme kanseri; progresyonsuz sağkalım; yaşlı hastalar.