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First-Line Treatment and Survival in Women Aged ≥ 70 Years with De Novo Hormone Receptor-Positive/Human Epidermal Growth Factor Receptor 2-Negative Metastatic Breast Cancer: A Multicenter Cohort Study by the Turkish Oncology Group

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Abstract

Background: Real-world evidence regarding first-line treatment selection and clinical outcomes in women aged 70 years and older with de novo hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2−) metastatic breast cancer remains limited. This study evaluated treatment patterns, survival outcomes, and treatment-related adverse events in this population. **Methods:** This multicenter retrospective study included 181 women aged ≥ 70 years with de novo HR+/HER2− metastatic breast cancer treated at 14 oncology centers in Türkiye between January 2016 and January 2026. Patients receiving first-line cyclin-dependent kinase 4/6 inhibitors plus aromatase inhibitors (CDK4/6i + AI; $n = 136$) were compared with those receiving other first-line regimens ($n = 45$). Treatment selection was evaluated using logistic regression, while progression-free survival (PFS) and overall survival (OS) were analyzed using Kaplan–Meier estimates and Cox regression. **Results:** CDK4/6i + AI was administered to 75.1% of patients. ECOG performance status ≥ 2 was independently associated with lower odds of receiving combination treatment (adjusted odds ratio [aOR], 0.24; $p = 0.003$), whereas higher baseline left ventricular ejection fraction was associated with greater treatment receipt (aOR per

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5-percentage-point increase, 1.62; $p = 0.002$). Median PFS was significantly longer with CDK4/6i + AI than with other treatments (43.6 vs. 12.9 months; $p < 0.001$), and this association persisted after adjustment, including HER2 status (adjusted hazard ratio [aHR], 0.48; 95% CI, 0.27–0.86; $p = 0.013$). No significant OS difference was observed (48.9 vs. 46.1 months; $p = 0.205$). Neutropenia was more frequent with CDK4/6i + AI (70.6% vs. 31.1%; $p < 0.001$). Recorded renal adverse events were also more frequent (12.5% vs. 0%; $p = 0.008$), although these could not be reliably distinguished from isolated creatinine elevations. **Conclusions:** First-line CDK4/6i + AI therapy was associated with longer PFS, without a significant OS difference, in older women with de novo HR+/HER2− metastatic breast cancer. Treatment selection was associated with functional status and cardiac function, supporting individualized therapeutic decisions beyond chronological age.

Keywords: metastatic breast cancer; CDK4/6 inhibitors; older adults; de novo metastatic disease; progression-free survival

1. Introduction

Hormone receptor-positive (HR+) and human epidermal growth factor receptor 2-negative (HER2−) breast cancer is the most prevalent biological subtype of breast cancer and constitutes a substantial proportion of metastatic cases. The introduction of cyclin-dependent kinase 4/6 (CDK4/6) inhibitors has transformed the treatment landscape of HR+/HER2− metastatic breast cancer. When combined with endocrine therapy, these agents have demonstrated substantial benefits in progression-free survival (PFS), with overall survival (OS) improvements reported for certain regimens. Consequently, CDK4/6 inhibitor-based endocrine therapy has become a standard first-line approach for most patients who do not require immediate chemotherapy [1–3].

Despite these advances, the optimal management of older patients remains challenging. Women aged ≥ 70 years often have multiple comorbidities, polypharmacy, functional impairments, and age-related physiological changes, all of which may affect treatment selection, tolerability, and clinical outcomes. Furthermore, older adults, particularly those with frailty or a substantial comorbidity burden, are underrepresented in clinical trials. This underrepresentation limits the generalizability of clinical trial findings to the heterogeneous older population encountered in routine oncology practice.

Recent real-world studies have provided insights into the use of CDK4/6 inhibitors in older patients with HR+/HER2− metastatic breast cancer. Multicenter observational data have demonstrated the feasibility and favorable clinical outcomes associated with these treatments in patients aged ≥ 70 years, although treatment-related toxicities and the need for dose modifications remain important considerations [4]. Other observational studies have reported favorable survival outcomes with CDK4/6 inhibitor-based regimens, particularly when combined with aromatase inhibitors, underscoring the importance of individualized treatment decisions [5]. Studies involving patients aged ≥ 80 years have further emphasized the role of functional status, comorbidities, and treatment tolerability in guiding systemic therapy selection [6].

Studies conducted in Türkiye have also contributed to the growing body of evidence on CDK4/6 inhibitor-based treatment in metastatic breast cancer. A large multicenter study by the Turkish Oncology Group evaluated ribociclib and palbociclib combined with fulvestrant in patients with HR+/HER2− metastatic breast cancer, providing valuable insights into treatment outcomes in routine clinical practice [7]. However, data specifically evaluating first-line aromatase inhibitor-based combinations in older adults remain scarce.

Beyond treatment selection, the identification of prognostic factors is important for optimizing clinical management. Disease burden, performance status, other clinical characteristics, and laboratory-based markers may offer complementary prognostic information. Recent research on the lactate dehydrogenase-to-albumin ratio and Glasgow Prognostic Score in patients receiving CDK4/6 inhibitors has further demonstrated the potential value of readily available biochemical and inflammatory markers for prognostic assessment [8].

Nevertheless, limited evidence is available on first-line treatment selection and comparative outcomes specifically in women aged ≥ 70 years with de novo HR+/HER2− metastatic breast cancer. Most real-world investigations have primarily evaluated patients treated with CDK4/6 inhibitors, whereas direct comparisons with alternative first-line regimens remain relatively uncommon. Moreover, the associations of baseline clinical characteristics with treatment selection, survival, and treatment-related adverse events warrant further investigation in this population.

Therefore, this multicenter retrospective study aimed to characterize first-line systemic treatment patterns, identify factors associated with the receipt of CDK4/6 inhibitor plus aromatase inhibitor therapy (CDK4/6i + AI), and evaluate OS, PFS, and treatment-related adverse events in women aged ≥ 70 years with de novo HR+/HER2− metastatic breast cancer across oncology centers in Türkiye.

2. Materials and Methods

2.1. Study Design and Patient Population

This multicenter, retrospective, observational cohort study was conducted across 14 oncology centers in Türkiye to evaluate first-line systemic treatment patterns, survival outcomes, and treatment-related adverse events among women aged 70 years or older with de novo metastatic HR+/HER2− breast cancer.

Patients who initiated first-line systemic treatment between January 2016 and January 2026 were retrospectively evaluated. A total of 181 patients were included in the final study population.

The inclusion criteria were age ≥ 70 years at diagnosis, histologically confirmed HR+/HER2− breast cancer, distant metastatic disease at initial diagnosis, receipt of first-line systemic treatment, and availability of sufficient clinical and follow-up data for outcome assessment. Patients with recurrent metastatic disease following an earlier diagnosis of nonmetastatic breast cancer, HR-negative or HER2-positive tumors, or insufficient treatment and survival data were excluded.

De novo metastatic disease was defined as the presence of distant metastases at the time of initial breast cancer diagnosis. All treatment decisions were made by the treating oncologists as part of routine clinical practice, considering performance status, comorbidities, disease burden, clinical condition, and treatment availability. No study-specific treatment allocation or intervention was performed.

2.2. Data Collection and Clinical Variables

Demographic, clinical, pathological, laboratory, treatment-related, and follow-up data were retrospectively collected from institutional medical records across the participating centers.

Baseline demographic and clinical variables included age, body mass index (BMI), Eastern Cooperative Oncology Group performance status (ECOG PS), comorbidities, concomitant medication use, polypharmacy, left ventricular ejection fraction (LVEF), and QT interval. Polypharmacy was defined as the concurrent use of five or more medications. The most recent available cardiac assessments, including LVEF and QT interval measurements, obtained before the initiation of first-line systemic therapy were used as baseline values.

Tumor-related characteristics included histological subtype, estrogen receptor (ER) and progesterone receptor (PR) expression, Ki-67 proliferation index, molecular testing results, and sites of metastatic involvement. HER2-negative tumors were further classified as HER2-zero (Immunohistochemistry [IHC] 0) or HER2-low (IHC 1+ or IHC 2+/ISH-negative) based on the original pathology reports. Metastatic sites were categorized as bone, lung, liver, brain, and lymph node involvement. Available molecular testing results, including BRCA1, BRCA2, and PIK3CA alterations, were recorded.

A visceral crisis was identified based on documented severe organ dysfunction attributable to rapidly progressive malignancy, rather than the presence of visceral metastases alone. Classification was based on the clinical assessments recorded by the treating oncologists.

Baseline laboratory parameters included hemoglobin, platelet count, neutrophil count, lymphocyte count, serum albumin, C-reactive protein (CRP), and cancer antigen 15-3 (CA 15-3). The most recent available laboratory measurements obtained before the initiation of first-line systemic therapy were used as baseline values.

First-line systemic treatments were classified into four categories: CDK4/6i + AI, AI monotherapy, chemotherapy, and CDK4/6 inhibitor plus fulvestrant.

For the primary comparative analysis, patients were categorized into two groups: those receiving first-line CDK4/6i + AI ($n = 136$) and those receiving other first-line treatments ($n = 45$). The latter group comprised patients treated with AI monotherapy ($n = 32$), chemotherapy ($n = 9$), or CDK4/6 inhibitor plus fulvestrant ($n = 4$). The primary treatment groups were defined according to the study objective of evaluating the real-world selection and outcomes of first-line CDK4/6i + AI therapy, a guideline-preferred treatment strategy for patients with HR+/HER2− metastatic breast cancer. As the study population consisted exclusively of patients with de novo metastatic disease, CDK4/6i + AI was selected as the treatment group of primary interest. All remaining first-line regimens were categorized as other treatments to reflect alternative therapeutic approaches used in routine clinical practice. This grouping was based on the study objective rather than an assumption of therapeutic equivalence among the comparator regimens.

Secondary comparisons included CDK4/6i + AI versus AI monotherapy and any first-line CDK4/6 inhibitor-containing regimen versus regimens without a CDK4/6 inhibitor.

2.3. Study Outcomes and Follow-Up

The primary outcomes were OS and PFS.

OS was defined as the interval from the initiation of first-line systemic therapy to death from any cause. Patients who remained alive were censored at the date of their last documented follow-up.

PFS was defined as the interval from the initiation of first-line systemic therapy to the first documented disease progression or death from any cause, whichever occurred first. Patients without documented progression or death were censored at their last documented follow-up date, at which disease status was assessed.

Disease progression was determined based on clinical and radiological evaluations documented in institutional medical records. Survival status, progression dates, and follow-up information were obtained from the participating centers.

Follow-up duration was calculated from the initiation of first-line systemic therapy to death or the last documented follow-up. Median follow-up duration was estimated using the reverse Kaplan–Meier method, with deaths treated as censored observations and patients alive at their last follow-up treated as events. Patient-specific documented follow-up dates were used without applying a uniform administrative data cutoff date.

2.4. Assessment of Treatment-Related Adverse Events

Treatment-related adverse events occurring during first-line systemic therapy were retrospectively assessed using institutional medical records.

Adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0, based on the available clinical and laboratory documentation. For analysis, adverse events were categorized as Grade 1–2 or Grade 3–4.

Hematologic adverse events included anemia, neutropenia, and thrombocytopenia. Nonhematologic adverse events included cardiotoxicity, gastrointestinal toxicity, hepatic toxicity, renal toxicity, dermatologic toxicity, neuromusculoskeletal toxicity, and pulmonary toxicity. Renal adverse events were assessed based on available clinical and laboratory documentation. Isolated serum creatinine elevations could not be systematically distinguished from clinically confirmed kidney injury; therefore, recorded renal toxicity was not considered synonymous with confirmed acute kidney injury.

The frequency and severity of adverse events were evaluated according to first-line treatment group. For between-group comparisons, each adverse event was classified as present (any grade) or absent. Patients could experience more than one adverse event.

2.5. Statistical Analysis

Descriptive statistics were used to summarize demographic, clinical, pathological, laboratory, and treatment-related characteristics. Continuous variables were presented as mean ± standard deviation or median (interquartile range [IQR]), depending on their distribution, while categorical variables were expressed as frequencies and percentages.

The normality of continuous variables was assessed using the Shapiro–Wilk test. Between-group comparisons were performed using the independent-samples Student's *t*-test or Mann–Whitney U test for continuous variables, as appropriate. Categorical variables were compared using the Pearson chi-square test or Fisher's exact test, depending on expected cell frequencies.

Univariable and multivariable binary logistic regression analyses were performed to identify baseline factors associated with the receipt of first-line CDK4/6i + AI therapy compared with other first-line regimens. The multivariable logistic regression model included age, ECOG PS, presence of comorbidities, LVEF, ER expression, liver metastasis, and baseline platelet count. Age was modeled per 5-year increase, LVEF per 5-percentage-point increase, ER expression per 10-percentage-point increase, and platelet count per 100,000/μL increase. ECOG PS was categorized as 0–1 versus ≥ 2. Results were expressed as odds ratios (ORs) and adjusted odds ratios (aORs), with corresponding 95% confidence intervals (CIs).

OS and PFS were estimated using the Kaplan–Meier method, and survival distributions were compared using the log-rank test. Median survival times and corresponding 95% CIs were reported where estimable. The primary survival comparison was between patients receiving first-line CDK4/6i + AI and those receiving other first-line treatments. Secondary comparisons included CDK4/6i + AI versus AI monotherapy and any first-line CDK4/6 inhibitor-containing regimen versus regimens without a CDK4/6 inhibitor.

Univariable and multivariable Cox proportional hazards regression analyses were performed to evaluate factors associated with OS and PFS. The multivariable Cox models included age, ECOG PS, LVEF, liver metastasis, ER expression, first-line treatment group, calendar year of first-line treatment initiation, number of metastatic sites, and HER2 status (HER2-low vs. HER2-zero).

These covariates were included to account for potential confounding related to baseline demographic, clinical, and tumor characteristics, particularly the observed differences in ECOG PS and liver metastasis between treatment groups. Calendar year of treatment initiation was modeled as a continuous variable (per 1-year increase), and the number of

metastatic sites was modeled per additional involved site as a proxy for metastatic disease burden. HER2 status was included as a binary variable, with HER2-zero as the reference category. Age, LVEF, and ER expression were modeled using the same increments specified above. Results were reported as hazard ratios (HRs) and adjusted hazard ratios (aHRs), with corresponding 95% CIs.

To assess the robustness of the primary survival findings and address the heterogeneity of the comparator group, a sensitivity analysis restricted to patients receiving CDK4/6i + AI therapy or AI monotherapy was performed. Multivariable Cox regression models for OS and PFS were fitted using the same nine covariates and variable definitions as in the primary analyses. To evaluate potential center-related heterogeneity, an additional sensitivity analysis was conducted using Cox proportional hazards models stratified by participating center. This approach allowed center-specific baseline hazard functions while retaining the original eight covariates, excluding HER2 status.

Multivariable regression analyses were conducted using complete cases for the covariates included in each model. Between-group comparisons of treatment-related adverse events were performed using two-sided Fisher's exact tests, comparing the occurrence of any-grade toxicity (Grade 1–4) with the absence of recorded toxicity. No adjustment for multiple comparisons was applied to these exploratory safety analyses. Secondary survival comparisons were considered exploratory, and no adjustment for multiple testing was performed.

Statistical analyses were performed using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA) and R software version 4.6.0 (R Foundation for Statistical Computing, Vienna, Austria) through the RStudio integrated development environment version 2025.05.1+513 (Posit Software, PBC, Boston, MA, USA). All statistical tests were two-sided, and p-values < 0.05 were considered statistically significant.

2.6. Ethical Considerations

The study was initially approved by the Manisa Celal Bayar University Faculty of Medicine Health Sciences Ethics Committee on 25 February 2026 (Decision No. 20.478.486/3918). The subsequent extension of the study from a single-center to a multicenter design was approved by the same ethics committee on 14 September 2026 (Decision No. 20.478.486/4483).

The study period (January 2016–January 2026) refers to the retrospective period of first-line treatment initiation, whereas the ethics committee approvals obtained in 2026 authorized the retrospective evaluation of previously collected clinical data.

The study was conducted retrospectively using routinely collected clinical data, without any additional patient interventions or study-specific procedures. The requirement for individual informed consent was waived by the Ethics Committee, as specified in the approved study protocol, because of the retrospective, non-interventional nature of the study and the use of anonymized patient data. Patient confidentiality was maintained throughout the study. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

2.7. Use of Generative AI

During the preparation of this manuscript, the authors used ChatGPT (OpenAI, GPT-6) to assist with English language editing, grammatical correction, and improvement of readability. All AI-assisted modifications were reviewed and verified by the authors, who take full responsibility for the final content of the manuscript.

3. Results

3.1. Baseline Patient Characteristics and First-Line Treatment Patterns

A total of 181 women aged ≥ 70 years with de novo metastatic HR+/HER2− breast cancer were included in this multicenter study. First-line treatment consisted of a CDK4/6i + AI in 136 patients (75.1%), AI monotherapy in 32 (17.7%), chemotherapy in 9 (5.0%), and a CDK4/6 inhibitor combined with fulvestrant in 4 (2.2%). For the primary comparison, patients were categorized into the CDK4/6i + AI group (n = 136, 75.1%) and the other treatment group (n = 45, 24.9%). The median follow-up duration, estimated using the reverse Kaplan–Meier method, was 36.3 months (95% CI, 31.7–40.6 months). Baseline demographic, clinical, tumor, and laboratory characteristics according to first-line treatment selection are summarized in Table 1.

Table 1. Baseline demographic, clinical, tumor, and laboratory characteristics according to first-line treatment.

Characteristic	Overall (n = 181)	CDK4/6i + AI (n = 136)	Other Treatments (n = 45)	p-Value
Demographic characteristics				
Age, years	75 (71.5–79.6)	74.3 (71.6–79.2)	77.3 (70.8–79.9)	0.595
Age categories				0.480
70–74 years	90 (49.7)	71 (52.2)	19 (42.2)	
75–79 years	50 (27.6)	35 (25.7)	15 (33.3)	
≥80 years	41 (22.7)	30 (22.1)	11 (24.4)	
BMI, kg/m^2	26.9 (24.3–30.8)	27.2 (24.6–30.5)	25.5 (23.6–31.3)	0.222
Performance status and comorbidities				
ECOG PS ≥ 2	38 (21)	19 (14)	19 (42.2)	<0.001
Presence of comorbidities	146 (80.7)	111 (81.6)	35 (77.8)	0.572
Polypharmacy (≥5 medications)	41 (22.7)	27 (19.9)	14 (31.1)	0.118
LVEF, %	60 (55–60)	60 (55–60)	55 (50–60)	<0.001
Baseline QT interval, ms	410 (394–430)	410 (394.8–431)	410 (390–420)	0.383
Tumor characteristics				
Invasive ductal carcinoma	148 (81.8)	114 (83.8)	34 (75.6)	0.213
Invasive lobular carcinoma	21 (11.6)	14 (10.3)	7 (15.6)	0.339
ER expression, %	90 (80–100)	90 (80–100)	80 (70–95)	0.016
PR expression, %	50 (20–80)	50 (20–86.2)	40 (10–80)	0.222
Ki-67 index, %	15 (10–25)	15 (10–25)	15 (10–30)	0.432
HER2 IHC status				0.085
IHC 0	109 (60.2)	77 (56.6)	32 (71.1)	
IHC 1+	42 (23.2)	33 (24.3)	9 (20.0)	
IHC 2+/ISH-negative	30 (16.6)	26 (19.1)	4 (8.9)	

Table 1. *Cont.*

Characteristic	Overall (n = 181)	CDK4/6i + AI (n = 136)	Other Treatments (n = 45)	p-Value
NGS status				0.075
Negative	65 (35.9)	45 (33.1)	20 (44.4)	
BRCA1 mutation	7 (3.9)	4 (2.9)	3 (6.7)	
BRCA2 mutation	2 (1.1)	2 (1.5)	0 (0)	
PIK3CA mutation	1 (0.6)	0 (0)	1 (2.2)	
BRCA2 + PIK3CA co-mutation	1 (0.6)	1 (0.7)	0 (0)	
Not tested	105 (58)	84 (61.8)	21 (46.7)	
Metastatic disease characteristics				
Bone metastasis	133 (73.5)	103 (75.7)	30 (66.7)	0.232
Lung metastasis	73 (40.3)	54 (39.7)	19 (42.2)	0.765
Liver metastasis	30 (16.6)	18 (13.2)	12 (26.7)	0.036
Brain metastasis	6 (3.3)	4 (2.9)	2 (4.4)	0.639
Lymph node metastasis	133 (73.5)	101 (74.3)	32 (71.1)	0.678
Visceral crisis	5 (2.8)	5 (3.7)	0 (0)	0.334
Baseline laboratory parameters				
Neutrophil count,/μL	4310 (3300–5600)	4315 (3310–5627.5)	4240 (3200–5300)	0.817
Lymphocyte count,/μL	1800 (1300–2350)	1800 (1322.5–2312.5)	1800 (1000–2400)	0.519
Hemoglobin, g/dL	12 (11–13)	12 (11.1–13.2)	11.5 (10.4–13)	0.064
Platelet count,/μL	269,000 (213,000–342,000)	280,000 (221,750–345,000)	234,000 (186,000–338,000)	0.016
Albumin, g/dL	4 (3.8–4.1)	4 (3.8–4.1)	4 (3.7–4.2)	0.482
CRP, mg/L	4 (2–9.4)	4.1 (2–8.6)	3 (1–13)	0.290
CA 15-3, U/mL	39 (24–75)	38.5 (22–70.4)	40 (24.1–119)	0.409

Values are presented as median (interquartile range) or n (%), as appropriate. Between-group comparisons were performed using the Mann–Whitney U test for continuous variables and the chi-square test or Fisher's exact test for categorical variables, as appropriate. Percentages were calculated based on available data for each variable. For HER2 status, the p-value was calculated by comparing HER2-zero (IHC 0) with HER2-low (IHC 1+ or IHC 2+/ISH-negative) using the Pearson chi-square test. For molecular testing (NGS), a single p-value was calculated to compare testing status (tested vs. not tested) between treatment groups using the Pearson chi-square test. Individual molecular alteration categories were presented descriptively without separate statistical comparisons. Percentages for molecular testing categories were calculated using the total number of patients in each respective group. Bold text indicates section headings within the table. Abbreviations: AI, aromatase inhibitor; BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status; LVEF, left ventricular ejection fraction; QT interval, time from the onset of the QRS complex to the end of the T wave on an electrocardiogram;ER, estrogen receptor; PR, progesterone receptor; CRP, C-reactive protein; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; NGS, next-generation sequencing.

The median age of the overall cohort was 75.0 years (IQR, 71.5–79.6). Overall, 90 patients (49.7%) were aged 70–74 years, 50 (27.6%) were aged 75–79 years, and 41 (22.7%) were aged ≥ 80 years. Median age was 74.3 years (IQR, 71.6–79.2) in the CDK4/6i + AI group and 77.3 years (IQR, 70.8–79.9) in the other treatment group, without a statistically significant difference (p = 0.595). BMI was also comparable between groups (p = 0.222).

Patients receiving CDK4/6i + AI had significantly better baseline performance status. An ECOG PS ≥ 2 was observed in 14.0% of patients receiving CDK4/6i + AI compared with 42.2% of those receiving other treatments ($p < 0.001$). Comorbidities were common, affecting 146 patients (80.7%), without a significant difference between treatment groups (81.6% vs. 77.8%; $p = 0.572$). Similarly, polypharmacy, defined as the concurrent use of ≥5 medications, was comparable between groups (19.9% vs. 31.1%; $p = 0.118$). Baseline LVEF was significantly higher in the CDK4/6i + AI group (median, 60% vs. 55%; $p < 0.001$), whereas baseline QT intervals did not differ significantly ($p = 0.383$).

Invasive ductal carcinoma was the predominant histological subtype (81.8%), followed by invasive lobular carcinoma (11.6%) and other histological subtypes (6.6%). ER expression was significantly higher in the CDK4/6i + AI group than in the other treatment group (median, 90% vs. 80%; $p = 0.016$). No statistically significant differences were observed in PR expression or Ki-67 proliferation index ($p = 0.222$ and $p = 0.432$, respectively). Regarding HER2 IHC status, 109 patients (60.2%) were classified as HER2-zero (IHC 0), while 72 (39.8%) had HER2-low disease, including 42 (23.2%) with IHC 1+ and 30 (16.6%) with IHC 2+/ISH-negative status. HER2-low disease was numerically more frequent in the CDK4/6i + AI group than in the other treatment group (43.4% vs. 28.9%), although the difference was not statistically significant ($p = 0.085$).

Next-generation sequencing (NGS) was performed in 76 patients (42.0%), while 105 patients (58.0%) had not undergone molecular testing. Among tested patients, 65 (85.5%) had negative results, whereas 11 (14.5%) had documented molecular alterations, including BRCA1, BRCA2, and PIK3CA mutations.

Bone and lymph nodes were the most frequently involved metastatic sites (73.5% each), followed by the lungs (40.3%) and liver (16.6%). Liver metastases were significantly more frequent among patients receiving other treatments than among those receiving CDK4/6i + AI (26.7% vs. 13.2%; $p = 0.036$). No statistically significant differences were observed in the distribution of other metastatic sites. Visceral crisis, as documented by the treating oncologists according to established clinical criteria, was present in five patients (2.8%), all of whom received first-line CDK4/6i + AI.

Regarding baseline laboratory parameters, platelet counts were significantly higher in the CDK4/6i + AI group than in the other treatment group (median, 280,000/μL vs. 234,000/μL; $p = 0.016$). Hemoglobin levels were numerically higher in the CDK4/6i + AI group, although the difference was not statistically significant (median, 12.0 vs. 11.5 g/dL; $p = 0.064$). No statistically significant differences were observed in neutrophil count, lymphocyte count, serum albumin, CRP, or CA 15-3 levels between treatment groups.

3.2. Factors Associated with First-Line Treatment Selection

Univariable and multivariable logistic regression analyses were performed to identify factors associated with receipt of first-line CDK4/6i + AI therapy. Patients receiving CDK4/6i + AI ($n = 136$) were compared with those receiving other first-line treatment regimens ($n = 45$). The results are presented in Table 2.

Table 2. Univariable and Multivariable Logistic Regression Analyses of Factors Associated with First-Line CDK4/6 Inhibitor Plus Aromatase Inhibitor Use.

Variable	Univariable OR (95% CI)	*p*	Multivariable aOR (95% CI)	*p*
Demographiccharacteristics				
Age (per 5-year increase)	0.86 (0.63–1.18)	0.353	1.14 (0.76–1.70)	0.531
BMI (per 5 kg/m^2 increase)	1.09 (0.77–1.56)	0.618		

Table 2. *Cont.*

Variable	Univariable OR (95% CI)	*p*	Multivariable aOR (95% CI)	*p*
Clinical characteristics				
ECOG PS ≥ 2 vs. 0–1	0.22 (0.10–0.48)	<0.001	0.24 (0.09–0.62)	0.003
Presence of comorbidities	1.27 (0.56–2.90)	0.572	2.18 (0.82–5.81)	0.120
Concomitant medications (per drug)	0.91 (0.77–1.08)	0.271		
Polypharmacy (≥5 medications)	0.55 (0.26–1.17)	0.121		
LVEF (per 5-percentage-point increase)	1.78 (1.35–2.35)	<0.001	1.62 (1.20–2.18)	0.002
QT interval (per 10 ms increase)	1.04 (0.94–1.15)	0.489		
Tumor characteristics				
Invasive lobular histology	0.62 (0.23–1.66)	0.343		
ER expression (per 10% increase)	1.21 (1.01–1.44)	0.034	1.18 (0.98–1.44)	0.084
PR expression (per 10% increase)	1.06 (0.96–1.17)	0.236		
Ki-67 index (per 10% increase)	0.89 (0.71–1.10)	0.280		
Metastatic involvement				
Lung	0.90 (0.45–1.79)	0.766		
Liver	0.42 (0.18–0.96)	0.039	0.43 (0.16–1.13)	0.086
Bone	1.56 (0.75–3.25)	0.234		
Brain	0.65 (0.12–3.68)	0.628		
Lymph node	1.17 (0.55–2.48)	0.678		
Baseline laboratory parameters				
Hemoglobin (per 1 g/dL)	1.21 (0.98–1.48)	0.077		
Platelet count (per 100,000/μL)	1.50 (1.01–2.21)	0.042	1.51 (0.99–2.31)	0.059
Neutrophil count (per 1000/μL)	1.03 (0.87–1.22)	0.721		
Lymphocyte count (per 1000/μL)	0.97 (0.66–1.44)	0.897		
Albumin (per 1 g/dL)	1.08 (0.43–2.76)	0.865		
CRP (per 10 units)	1.00 (0.78–1.28)	0.988		
CA 15-3 (per 100 units)	1.07 (0.76–1.52)	0.698		

Values are presented as odds ratios (ORs) and adjusted odds ratios (aORs) with corresponding 95% confidence intervals (CIs). Univariable and multivariable logistic regression analyses were performed to identify factors associated with first-line CDK4/6i plus AI use. The multivariable model included age, ECOG performance status, presence of comorbidities, LVEF, ER expression, liver metastasis, and baseline platelet count. Multivariable analysis was performed using complete cases for the included covariates. All *p*-values are two-sided, and $p < 0.05$ was considered statistically significant. Abbreviations: BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group Performance Status; LVEF, left ventricular ejection fraction; QT interval, time from the onset of the QRS complex to the end of the T wave on an electrocardiogram; ER, estrogen receptor; PR, progesterone receptor; CRP, C-reactive protein; CA 15-3, cancer antigen 15-3.

In univariable analysis, ECOG PS ≥ 2 was significantly associated with lower odds of receiving CDK4/6i + AI therapy (OR, 0.22; 95% CI, 0.10–0.48; $p < 0.001$). Liver metastasis was also associated with lower odds of treatment receipt (OR, 0.42; 95% CI, 0.18–0.96; $p = 0.039$). Conversely, higher LVEF (OR per 5-percentage-point increase, 1.78; 95% CI, 1.35–2.35; $p < 0.001$), higher ER expression (OR per 10-percentage-point increase, 1.21; 95% CI, 1.01–1.44; $p = 0.034$), and

higher baseline platelet count (OR per 100,000/μL increase, 1.50; 95% CI, 1.01–2.21; $p = 0.042$) were significantly associated with increased odds of receiving CDK4/6i + AI therapy. No statistically significant associations were observed for the remaining variables, including age, BMI, comorbidity status, concomitant medication use, and polypharmacy.

In multivariable analysis adjusted for age, ECOG PS, comorbidity status, LVEF, ER expression, liver metastasis, and platelet count, ECOG PS ≥ 2 remained significantly associated with lower odds of receiving CDK4/6i + AI therapy (aOR, 0.24; 95% CI, 0.09–0.62; $p = 0.003$). Higher LVEF also remained significantly associated with treatment receipt (aOR per 5-percentage-point increase, 1.62; 95% CI, 1.20–2.18; $p = 0.002$). Age, comorbidity status, ER expression, and liver metastasis were not significantly associated with treatment receipt after adjustment. Although higher baseline platelet count showed a positive association, it did not reach statistical significance (aOR per 100,000/μL increase, 1.51; 95% CI, 0.99–2.31; $p = 0.059$).

3.3. Overall and Progression-Free Survival According to First-Line Treatment

OS and PFS were evaluated according to first-line treatment selection using Kaplan–Meier survival analysis. Three comparisons were performed: CDK4/6i + AI versus other first-line treatments, CDK4/6i + AI versus AI monotherapy, and any CDK4/6 inhibitor-containing regimen versus regimens without a CDK4/6 inhibitor.

In the primary comparison, 136 patients receiving CDK4/6i + AI were compared with 45 patients receiving other first-line treatments. During follow-up, 69 deaths were recorded, including 39 in the CDK4/6i + AI group and 30 in the other treatment group. Median OS was 48.9 months (95% CI, 42.1–not estimable) in the CDK4/6i + AI group and 46.1 months (95% CI, 26.0–66.8) in the other treatment group, with no statistically significant difference (log-rank $p = 0.205$; Figure 1A). In univariable Cox regression analysis, CDK4/6i + AI use was associated with an HR for death of 0.72 (95% CI, 0.44–1.20; $p = 0.206$). In contrast, median PFS was significantly longer in the CDK4/6i + AI group than in the other treatment group (43.6 months [95% CI, 25.4–not estimable] vs. 12.9 months [95% CI, 8.6–20.5]; log-rank $p < 0.001$; Figure 1B). The corresponding univariable HR for progression or death was 0.36 (95% CI, 0.24–0.55; $p < 0.001$).

In a secondary analysis restricted to patients receiving CDK4/6i + AI ($n = 136$) or AI monotherapy ($n = 32$), median OS was 48.9 and 28.3 months, respectively, with a statistically significant difference between groups (log-rank $p = 0.018$; Figure 2A). Median PFS was also significantly longer among patients receiving CDK4/6i + AI than among those receiving AI monotherapy (43.6 vs. 14.5 months; log-rank $p < 0.001$; Figure 2B).

An additional analysis compared patients receiving any CDK4/6 inhibitor-containing regimen ($n = 140$) with those receiving regimens without a CDK4/6 inhibitor ($n = 41$). Median OS was 48.9 months in the CDK4/6 inhibitor group and 38.9 months in the non-CDK4/6 inhibitor group; however, the difference did not reach statistical significance (log-rank $p = 0.074$; Figure 3A). In contrast, median PFS was significantly longer in patients receiving CDK4/6 inhibitor-containing treatment (43.6 vs. 12.9 months; log-rank $p < 0.001$; Figure 3B). During follow-up, 65 patients (35.9%) received second-line systemic treatment, including 31 patients (22.8%) in the CDK4/6i + AI group and 34 patients (75.6%) in the other first-line treatment group. Information regarding second-line treatment receipt was unavailable for two patients.

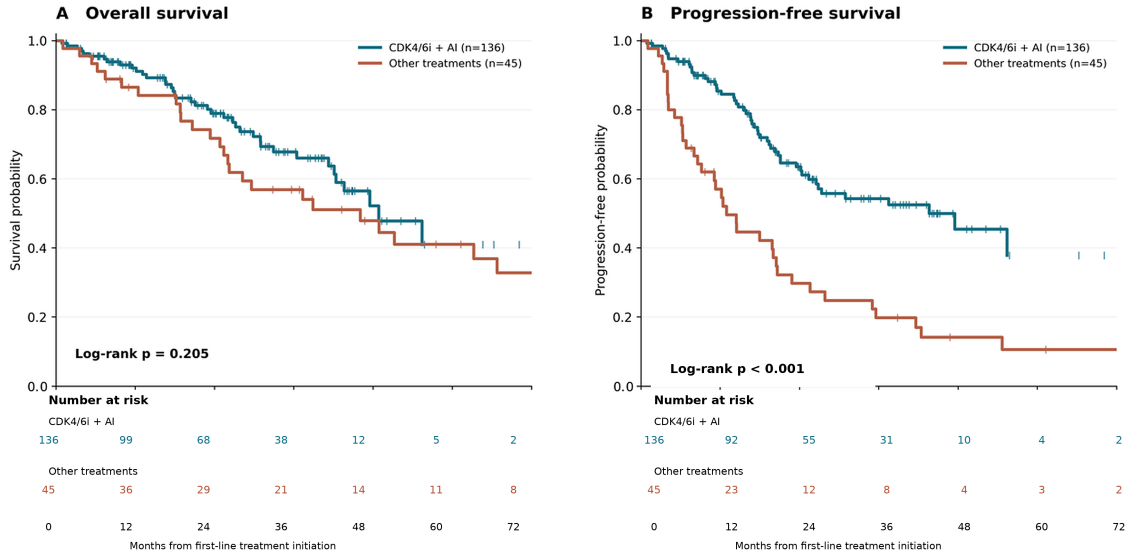


Figure 1. Overall Survival and Progression-Free Survival According to First-Line Treatment (CDK4/6i + AI vs. Other Treatments).

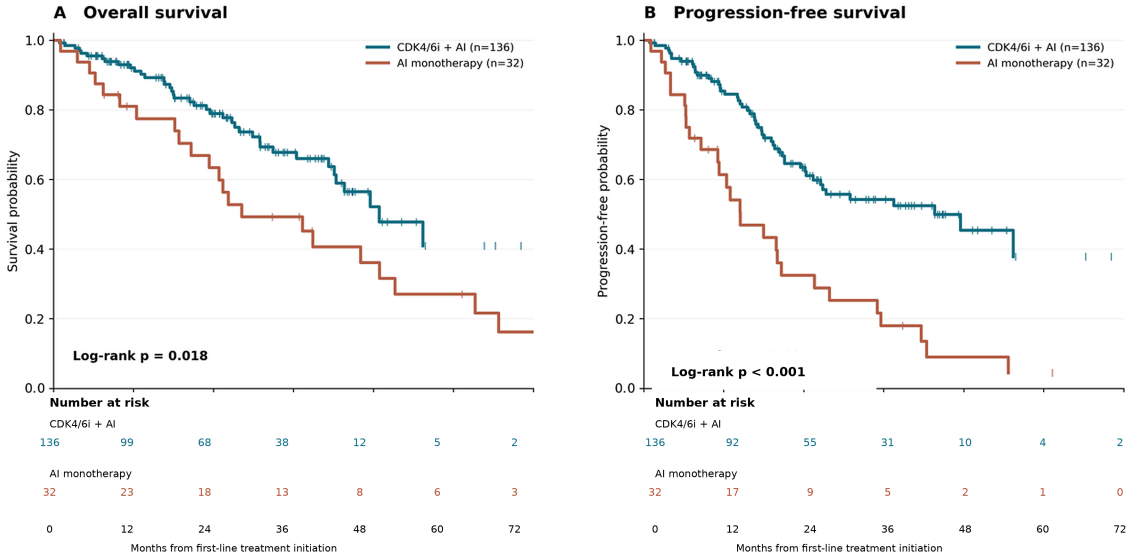


Figure 2. Overall Survival and Progression-Free Survival in Patients Receiving CDK4/6i + AI Versus AI Monotherapy.

3.4. Factors Associated with Overall and Progression-Free Survival

Univariable and multivariable Cox proportional hazards regression analyses were performed to identify factors associated with OS and PFS (Table 3). The multivariable models included nine covariates: age, ECOG PS, LVEF, liver metastasis, ER expression, first-line treatment group, calendar year of treatment initiation, number of metastatic sites, and HER2 status (HER2-low vs. HER2-zero).

In the univariable analysis for OS, increasing age (HR per 5-year increase, 1.65; 95% CI, 1.33–2.05; $p < 0.001$) and ECOG PS ≥ 2 (HR, 2.26; 95% CI, 1.34–3.81; $p = 0.002$) were significantly associated with a higher risk of death, whereas higher LVEF was associated with a lower risk (HR per 5-percentage-point increase, 0.68; 95% CI, 0.56–0.82; $p < 0.001$). Treatment initiation year was also significantly associated with OS (HR per year, 1.15; 95% CI, 1.02–1.30; $p = 0.022$). HER2-low status was not significantly associated with OS (HR, 1.04; 95% CI, 0.63–1.71; $p = 0.873$).

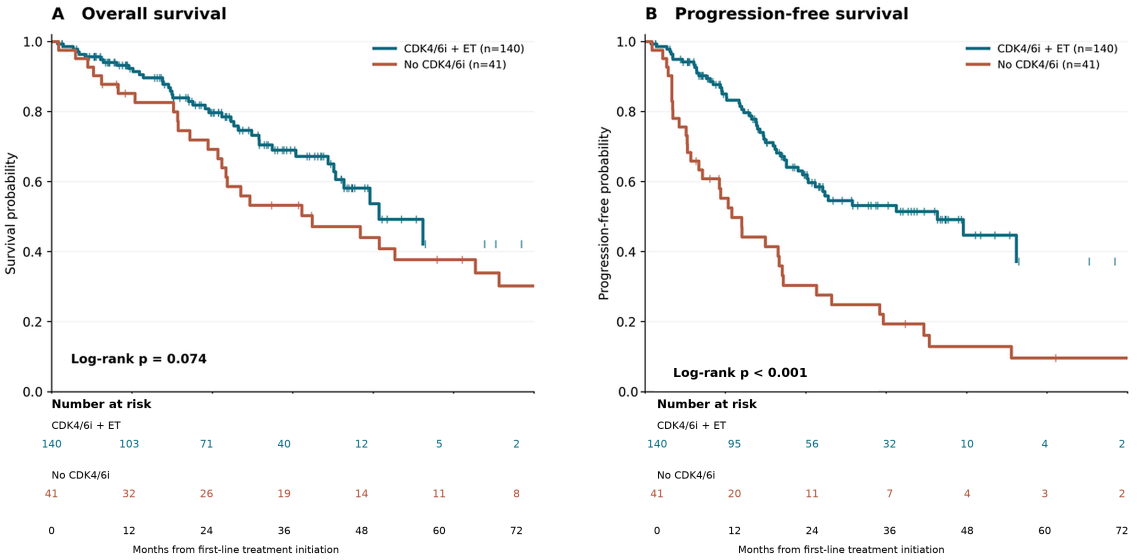


Figure 3. Overall Survival and Progression-Free Survival According to First-Line CDK4/6 Inhibitor Use.

In the multivariable analysis for OS, increasing age remained independently associated with a higher risk of death (aHR per 5-year increase, 1.61; 95% CI, 1.27–2.03; $p < 0.001$), while higher LVEF remained associated with a lower risk (aHR per 5-percentage-point increase, 0.76; 95% CI, 0.61–0.96; $p = 0.022$). Greater ER expression was also associated with a lower hazard of death (aHR per 10% increase, 0.87; 95% CI, 0.76–1.00; $p = 0.049$), whereas later calendar year of treatment initiation was associated with a higher hazard (aHR per year, 1.19; 95% CI, 1.03–1.38; $p = 0.020$). First-line CDK4/6i + AI therapy was not significantly associated with OS after adjustment (aHR, 0.83; 95% CI, 0.44–1.59; $p = 0.576$). HER2-low status was likewise not significantly associated with OS (aHR, 0.76; 95% CI, 0.44–1.32; $p = 0.330$).

In the univariable analysis for PFS, increasing age (HR per 5-year increase, 1.32; 95% CI, 1.09–1.60; $p = 0.005$), ECOG PS ≥ 2 (HR, 1.73; 95% CI, 1.07–2.80; $p = 0.024$), and liver metastasis (HR, 1.97; 95% CI, 1.22–3.17; $p = 0.005$) were significantly associated with a higher risk of progression or death. Conversely, higher LVEF (HR per 5-percentage-point increase, 0.77; 95% CI, 0.66–0.90; $p = 0.001$), greater ER expression (HR per 10% increase, 0.88; 95% CI, 0.79–0.97; $p = 0.008$), and first-line CDK4/6i + AI therapy (HR, 0.36; 95% CI, 0.24–0.55; $p < 0.001$) were associated with a lower risk of progression or death. HER2-low status was not significantly associated with PFS (HR, 0.81; 95% CI, 0.52–1.26; $p = 0.356$).

In the multivariable analysis for PFS, first-line CDK4/6i + AI therapy remained significantly associated with a lower risk of progression or death compared with other first-line treatments (aHR, 0.48; 95% CI, 0.27–0.86; $p = 0.013$). Increasing age was independently associated with a higher risk of progression or death (aHR per 5-year increase, 1.27; 95% CI, 1.03–1.56; $p = 0.024$), whereas greater ER expression was associated with a lower risk (aHR per 10% increase, 0.88; 95% CI, 0.78–0.99; $p = 0.037$). Liver metastasis was not significantly associated with PFS after multivariable adjustment (aHR, 1.60; 95% CI, 0.92–2.80; $p = 0.098$). HER2-low status was also not significantly associated with PFS (aHR, 0.72; 95% CI, 0.44–1.19; $p = 0.202$). ECOG PS, LVEF, calendar year of treatment initiation, and number of metastatic sites were not significantly associated with PFS after adjustment.

Table 3. Univariable and Multivariable Cox Regression Analyses for Overall and Progression-Free Survival.

Variables	OS				PFS			
	Univ. HR (95% CI)	*p*-Value	Multiv. aHR (95% CI)	*p*-Value	Univ. HR (95% CI)	*p*-Value	Multiv. aHR (95% CI)	*p*-Value
Age (per 5-year increase)	1.65 (1.33–2.05)	<0.001	1.61 (1.27–2.03)	<0.001	1.32 (1.09–1.60)	0.005	1.27 (1.03–1.56)	0.024
ECOG ≥ 2 vs. 0–1	2.26 (1.34–3.81)	0.002	1.31 (0.72–2.37)	0.377	1.73 (1.07–2.80)	0.024	1.13 (0.65–1.96)	0.673
LVEF (per 5-percentage-point increase)	0.68 (0.56–0.82)	<0.001	0.76 (0.61–0.96)	0.022	0.77 (0.66–0.90)	0.001	0.89 (0.73–1.09)	0.273
Liver metastasis (yes vs. no)	1.25 (0.70–2.21)	0.453	1.32 (0.70–2.50)	0.387	1.97 (1.22–3.17)	0.005	1.60 (0.92–2.80)	0.098
ER expression (per 10% increase)	0.89 (0.79–1.01)	0.062	0.87 (0.76–1.00)	0.049	0.88 (0.79–0.97)	0.008	0.88 (0.78–0.99)	0.037
CDK4/6i + AI vs. other treatments	0.72 (0.44–1.20)	0.206	0.83 (0.44–1.59)	0.576	0.36 (0.24–0.55)	<0.001	0.48 (0.27–0.86)	0.013
Treatment initiation year (per year)	1.15 (1.02–1.30)	0.022	1.19 (1.03–1.38)	0.020	0.97 (0.89–1.05)	0.449	1.04 (0.93–1.16)	0.512
Number of metastatic sites (per site)	1.09 (0.83–1.43)	0.525	0.96 (0.70–1.31)	0.782	1.20 (0.94–1.52)	0.149	1.05 (0.80–1.40)	0.714
HER2-low vs. HER2-zero	1.04 (0.63–1.71)	0.873	0.76 (0.44–1.32)	0.330	0.81 (0.52–1.26)	0.356	0.72 (0.44–1.19)	0.202

Values are presented as hazard ratios (HRs) and adjusted hazard ratios (aHRs) with corresponding 95% confidence intervals (CIs). Univariable and multivariable Cox proportional hazards regression analyses were performed for overall survival (OS) and progression-free survival (PFS). Multivariable models included nine covariates: age, ECOG performance status, LVEF, liver metastasis, ER expression, first-line treatment group, calendar year of treatment initiation, number of metastatic sites, and HER2 status (HER2-low vs. HER2-zero). All 181 patients had complete data for the covariates included in the multivariable Cox regression models. Age was analyzed per 5-year increase, LVEF per 5-percentage-point increase, ER expression per 10-percentage-point increase, treatment initiation year per 1-year increase, and number of metastatic sites per additional involved site. Reference categories were ECOG 0–1, absence of liver metastasis, other first-line treatments, and HER2-zero (IHC 0). HER2-low was defined as IHC 1+ or IHC 2+/ISH-negative. All *p*-values are two-sided. Abbreviations: HR, hazard ratio; aHR, adjusted hazard ratio; CI, confidence interval; OS, overall survival; PFS, progression-free survival; ECOG, Eastern Cooperative Oncology Group; LVEF, left ventricular ejection fraction; ER, estrogen receptor; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; AI, aromatase inhibitor; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization.

3.5. Sensitivity Analysis

To assess the robustness of the primary findings and address the heterogeneity of the comparator group, an additional multivariable Cox regression analysis was performed comparing patients receiving first-line CDK4/6i + AI ($n = 136$) with those receiving AI monotherapy ($n = 32$). After adjustment for the same nine covariates used in the primary model, including HER2 status, CDK4/6i + AI therapy was associated with a numerically lower hazard of progression or death, although the association did not reach statistical significance (aHR, 0.62; 95% CI, 0.32–1.18; $p = 0.143$). No significant association was observed for OS (aHR, 0.76; 95% CI, 0.38–1.55; $p = 0.456$). Detailed results are provided in Supplementary Table S1.

In a center-stratified sensitivity analysis, the association between CDK4/6i + AI therapy and PFS remained directionally favorable but did not reach statistical significance (aHR, 0.54; 95% CI, 0.27–1.05; $p = 0.067$).

3.6. Treatment-Related Adverse Events

Treatment-related adverse events during first-line therapy were evaluated according to treatment group (Table 4). Neutropenia was the most frequently reported hematologic adverse event among patients receiving CDK4/6i + AI, with Grade 1–2 and Grade 3–4 neutropenia observed in 66 (48.5%) and 30 patients (22.1%), respectively. The overall incidence of neutropenia was significantly higher in the CDK4/6i + AI group than in the other treatment group (70.6% vs. 31.1%; $p < 0.001$). Anemia was observed in 51 (37.5%) and 12 patients (26.7%), respectively ($p = 0.210$), while thrombocytopenia occurred in 19 (14.0%) and 2 patients (4.4%), respectively ($p = 0.108$).

Among nonhematologic adverse events, gastrointestinal toxicity occurred in 23 patients (16.9%) receiving CDK4/6i + AI and 6 patients (13.3%) receiving other treatments ($p = 0.647$). Cardiotoxicity was reported in 14 (10.3%) and 1 patient (2.2%), respectively ($p = 0.121$). Hepatic toxicity occurred in 13 (9.6%) and 3 patients (6.7%), respectively ($p = 0.764$). Recorded renal adverse events were significantly more frequent in the CDK4/6i + AI group than in the comparator group (12.5% vs. 0%; $p = 0.008$). Conversely, neuromusculoskeletal toxicity was more frequent in the other treatment group (17.8% vs. 5.9%; $p = 0.029$). Dermatologic toxicity was observed in 5 (3.7%) and 2 patients (4.4%), respectively ($p = 1.000$), whereas pulmonary toxicity was reported in 2 patients (1.5%) receiving CDK4/6i + AI and none receiving other treatments ($p = 1.000$).

Table 4. First-Line Treatment-Related Adverse Events According to Treatment Group.

Adverse Event	CDK4/6i + AI ($n = 136$) Grade 1–2	Grade 3–4	Other Treatments ($n = 45$) Grade 1–2	Grade 3–4	*p* Value
Anemia	46 (33.8)	5 (3.7)	12 (26.7)	0 (0)	0.210
Neutropenia	66 (48.5)	30 (22.1)	10 (22.2)	4 (8.9)	<0.001
Thrombocytopenia	16 (11.8)	3 (2.2)	2 (4.4)	0 (0)	0.108
Cardiotoxicity	10 (7.4)	4 (2.9)	1 (2.2)	0 (0)	0.121
Gastrointestinal toxicity	21 (15.4)	2 (1.5)	5 (11.1)	1 (2.2)	0.647
Hepatic toxicity	13 (9.6)	0 (0)	2 (4.4)	1 (2.2)	0.764
Renal toxicity	14 (10.3)	3 (2.2)	0 (0)	0 (0)	0.008
Dermatologic toxicity	5 (3.7)	0 (0)	1 (2.2)	1 (2.2)	1.000
Neuromusculoskeletal toxicity	8 (5.9)	0 (0)	8 (17.8)	0 (0)	0.029
Pulmonary toxicity	2 (1.5)	0 (0)	0 (0)	0 (0)	1.000

Values are presented as *n* (%). Between-group comparisons were performed using the two-sided Fisher's exact test for any-grade adverse events (Grade 1–4 versus no adverse event). Patients could experience more than one adverse event. No adjustment for multiple comparisons was applied.

Grade 3–4 adverse events in the CDK4/6i + AI group were predominantly hematologic, particularly neutropenia (22.1%). Grade 3–4 cardiotoxicity, renal toxicity, gastrointestinal toxicity, anemia, and thrombocytopenia were less frequent, occurring in 2.9%, 2.2%, 1.5%, 3.7%, and 2.2% of patients, respectively. Among patients receiving first-line CDK4/6i + AI therapy, dose reductions were required in 42 patients (30.9%). Permanent treatment discontinuation attributed to toxicity was recorded in 12 patients (8.8%) with documented

toxicity-related reasons, including hematologic toxicity ($n = 3$), cardiotoxicity ($n = 2$), hepatic toxicity ($n = 1$), pulmonary toxicity ($n = 1$), and other recorded reasons ($n = 5$). These findings should be interpreted cautiously given the heterogeneous treatment regimens included in the comparator group.

4. Discussion

In this multicenter retrospective study of 181 women aged ≥ 70 years with de novo HR+/HER2− metastatic breast cancer, first-line CDK4/6i + AI therapy was associated with significantly longer PFS, but not OS, compared with alternative regimens. Treatment selection was influenced by performance status and cardiac function, while increasing age was associated with poorer survival. These findings support individualized treatment decisions in older patients.

CDK4/6i + AI was administered to 75.1% of patients, reflecting its widespread use in routine practice. However, recipients had more favorable baseline characteristics, including better ECOG PS, higher LVEF and ER expression, and fewer liver metastases, suggesting potential confounding by indication. Similar treatment selection patterns have been reported in real-world studies [9]. The comparator group included heterogeneous first-line regimens to reflect routine clinical practice. In a sensitivity analysis restricted to CDK4/6i + AI versus AI monotherapy, the PFS association remained directionally consistent but was no longer statistically significant after adjustment (Supplementary Table S1).

In multivariable logistic regression, ECOG PS ≥ 2 was independently associated with lower odds of receiving CDK4/6i + AI (aOR, 0.24; 95% CI, 0.09–0.62; $p = 0.003$), whereas higher LVEF was associated with greater treatment receipt (aOR per 5-percentage-point increase, 1.62; 95% CI, 1.20–2.18; $p = 0.002$). In contrast, chronological age, comorbidity status, ER expression, liver metastasis, and platelet count were not independently associated with treatment selection. These findings suggest that clinicians may have prioritized functional and cardiovascular characteristics over age alone when selecting combination treatment. However, the observational design does not allow determination of the specific reasons underlying individual treatment decisions.

Comorbidities and polypharmacy were present in 80.7% and 22.7% of patients, respectively, but neither differed significantly between treatment groups nor independently predicted CDK4/6i + AI use. However, these measures may not adequately reflect comorbidity severity, drug interactions, or geriatric vulnerabilities. Current recommendations emphasize incorporating functional, cognitive, nutritional, and social factors into treatment decisions [10]. Similarly, recent reviews highlight the importance of assessing frailty and treatment tolerability rather than chronological age alone when prescribing CDK4/6 inhibitors [11].

The primary efficacy finding was the marked difference in PFS. Median PFS was 43.6 months with CDK4/6i + AI compared with 12.9 months with other first-line treatments (log-rank $p < 0.001$). In multivariable Cox regression, combination treatment remained associated with a lower hazard of progression or death after additional adjustment for HER2 status (aHR, 0.48; 95% CI, 0.27–0.86; $p = 0.013$).

This finding is consistent with randomized trials demonstrating improved disease control with CDK4/6 inhibitors plus endocrine therapy [12–14]. Recent evidence syntheses also support the PFS benefit of these regimens in older patients, although safety concerns and the underrepresentation of frail individuals remain important limitations [15,16].

The relatively prolonged median PFS in our cohort warrants consideration. Previous real-world studies in older patients have reported variable PFS outcomes, reflecting differences in patient characteristics, treatment regimens, and study populations [4–6]. Our restriction to de novo metastatic disease may have reduced heterogeneity related to prior

endocrine exposure and resistance. However, favorable baseline characteristics, patient selection, disease burden, and retrospective progression assessment may also have contributed to the observed PFS. Cross-study comparisons are further limited by differences in follow-up and outcome assessment. Although median PFS in the CDK4/6i + AI group (43.6 months) exceeded the reverse Kaplan–Meier median follow-up (36.3 months), these estimates measure different aspects of the survival data and are not directly comparable. The non-estimable upper confidence limit further indicates uncertainty in the precision of the PFS estimate, warranting cautious interpretation.

Secondary analyses supported the primary PFS findings. CDK4/6i + AI versus AI monotherapy yielded median PFS of 43.6 versus 14.5 months ($p < 0.001$) and OS of 48.9 versus 28.3 months ($p = 0.018$). Comparing all CDK4/6 inhibitor-containing regimens with regimens without CDK4/6 inhibitors, median PFS was 43.6 versus 12.9 months ($p < 0.001$), while OS did not differ significantly (48.9 vs. 38.9 months; $p = 0.074$). However, these unadjusted, exploratory comparisons involved overlapping populations and lacked correction for multiple testing. Thus, the significant OS difference versus AI monotherapy should be considered hypothesis-generating rather than definitive.

To address comparator heterogeneity, a multivariable sensitivity analysis was restricted to CDK4/6i + AI versus AI monotherapy. After adjustment for nine covariates, including HER2 status, the PFS association remained directionally favorable but was not statistically significant (aHR, 0.62; 95% CI, 0.32–1.18; $p = 0.143$). No significant OS association was observed (aHR, 0.76; 95% CI, 0.38–1.55; $p = 0.456$). The smaller sample size and potential residual confounding warrant cautious interpretation.

In the center-stratified sensitivity analysis, the association between CDK4/6i + AI therapy and PFS remained directionally favorable but was no longer statistically significant (aHR, 0.54; 95% CI, 0.27–1.05; $p = 0.067$). This attenuation suggests that between-center differences may have influenced the estimated treatment association and highlights the need for cautious interpretation of the primary PFS findings.

In the primary comparison, median OS was 48.9 months in the CDK4/6i + AI group and 46.1 months in the comparator group, without a statistically significant difference ($p = 0.205$). After multivariable adjustment, including HER2 status, the treatment group was not significantly associated with OS (aHR, 0.83; 95% CI, 0.44–1.59; $p = 0.576$).

This finding differs from the significant OS improvement demonstrated with ribociclib plus letrozole in MONALEESA-2, where median OS was 63.9 versus 51.4 months [12]. However, OS results have not been uniform across first-line CDK4/6 inhibitor trials. The final PALOMA-2 analysis did not demonstrate a statistically significant OS improvement with palbociclib plus letrozole, despite the established PFS benefit [13]. Similarly, the final MONARCH 3 analysis showed a numerical OS improvement with abemaciclib plus a nonsteroidal aromatase inhibitor that did not meet the prespecified threshold for statistical significance [14]. These findings illustrate that improvements in PFS do not necessarily translate into statistically significant OS differences in every study or treatment setting.

The absence of a significant OS association in our study requires particularly cautious interpretation. Only 69 deaths were recorded during a median follow-up of 36.3 months, and the comparator group included just 45 patients receiving heterogeneous treatments. Subsequent systemic therapies, competing causes of death, and differences in baseline clinical characteristics may have influenced survival. Moreover, the wide confidence interval around the adjusted treatment effect does not establish equivalence between treatment strategies. Real-world evidence has also suggested that earlier CDK4/6 inhibitor use may delay subsequent treatment escalation without necessarily demonstrating a statistically significant OS difference [9]. Therefore, the present findings should be interpreted as evidence of an association with prolonged PFS rather than proof of an OS benefit or lack thereof.

The timing of CDK4/6 inhibitor initiation is also relevant to interpreting these results. The randomized SONIA trial compared first-line CDK4/6 inhibitor use with deferred introduction in the second-line setting and did not demonstrate a statistically significant improvement in PFS after two treatment lines in its primary analysis, while earlier treatment increased cumulative exposure and severe adverse events [17]. Importantly, this trial addressed treatment sequencing rather than the direct first-line PFS comparison evaluated in our study. Its findings nevertheless emphasize that the optimal timing of combination therapy should be considered in relation to the patient's clinical condition, anticipated treatment burden, and subsequent therapeutic options. Our data cannot determine whether selected older patients receiving initial endocrine monotherapy would achieve comparable long-term outcomes if CDK4/6 inhibitors were introduced later.

Increasing age was independently associated with both OS and PFS. Each 5-year increase in age was associated with a higher hazard of death (aHR, 1.61; 95% CI, 1.27–2.03; $p < 0.001$) and progression or death (aHR, 1.27; 95% CI, 1.03–1.56; $p = 0.024$). Importantly, age was not independently associated with treatment selection, indicating that its prognostic relevance was not simply reflected in the choice of first-line regimen. The stronger association with OS may partly reflect competing mortality risks and age-related physiological vulnerability, although cause-specific mortality was not available. These findings reinforce the importance of distinguishing chronological age as a prognostic characteristic from its use as an isolated treatment-selection criterion. Comprehensive geriatric assessment may help identify vulnerabilities not captured by ECOG performance status or conventional comorbidity measures [10,11].

Baseline LVEF was another notable factor. Higher LVEF was independently associated with lower mortality (aHR per 5-percentage-point increase, 0.76; 95% CI, 0.61–0.96; $p = 0.022$), but its adjusted association with PFS was not statistically significant. This difference suggests that cardiac function may reflect broader physiological reserve and competing health risks rather than tumor-specific treatment effectiveness. Nevertheless, LVEF should not be considered a validated predictive biomarker of CDK4/6 inhibitor benefit. The observed relationship may also be influenced by treatment-selection practices and unmeasured cardiovascular comorbidities. Although baseline QT intervals were comparable between groups, the retrospective design and absence of detailed agent-specific cardiac monitoring data limit further conclusions regarding cardiovascular risk.

ECOG PS ≥ 2 was associated with shorter OS and PFS in univariable analyses but did not retain statistical significance after adjustment. This attenuation may reflect correlations between functional impairment, age, cardiac function, and disease burden. Liver metastasis was more common in the alternative-treatment group and was associated with shorter PFS in univariable analysis. However, its association did not reach statistical significance after multivariable adjustment (aHR, 1.60; 95% CI, 0.92–2.80; $p = 0.098$). In contrast, higher ER expression remained significantly associated with a lower hazard of progression or death after adjustment (aHR per 10% increase, 0.88; 95% CI, 0.78–0.99; $p = 0.037$). These findings suggest that metastatic distribution and hormone receptor expression may contribute to prognosis, although their independent effects could not be conclusively established in this cohort. The predominance of bone and lymph node metastases, each observed in 73.5% of patients, also reflects the clinical heterogeneity of HR+/HER2− metastatic disease. Visceral crisis was documented in only five patients, precluding meaningful subgroup conclusions.

Baseline platelet counts were higher in the CDK4/6i + AI group and associated with treatment selection in univariable analysis, but not after adjustment (aOR, 1.51; 95% CI, 0.99–2.31; $p = 0.059$). Other laboratory parameters, including hemoglobin, neutrophils, lymphocytes, albumin, CRP, and CA 15-3, did not differ significantly between groups. However, these findings do not exclude their prognostic relevance, as treatment-group comparisons

do not assess survival associations. Previous studies have explored inflammatory and biochemical markers in patients receiving CDK4/6 inhibitors [8], including a combined CA 15-3 and neutrophil-to-lymphocyte ratio score in the neoadjuvant setting [18]. Nevertheless, these findings cannot be directly extrapolated to older patients with metastatic disease, and no combined biomarker score was validated in our cohort.

Molecular testing was performed in 42.0% of patients, with documented BRCA1, BRCA2, or PIK3CA alterations in a small proportion of the overall cohort. The limited testing rate and low number of detected alterations restricted the ability to evaluate molecularly defined subgroups. Furthermore, the absence of a documented alteration in untested patients cannot be interpreted as molecular negativity. These limitations highlight the challenges of retrospective molecular characterization across multiple institutions and prevent conclusions regarding genotype-specific treatment selection or survival.

HER2 expression was further characterized according to IHC status, with 39.8% of patients classified as HER2-low. HER2-low status was not significantly associated with OS or PFS in the adjusted Cox models. Importantly, the association between CDK4/6i + AI therapy and longer PFS persisted after adjustment for HER2 status. Nevertheless, the retrospective classification of HER2 expression and the lack of detailed information regarding subsequent HER2-directed therapies limit further interpretation.

Neutropenia was the most common treatment-related adverse event with CDK4/6i + AI, occurring in 70.6% of patients versus 31.1% in the alternative-treatment group ($p < 0.001$), with Grade 3–4 neutropenia reported in 22.1% of CDK4/6i + AI recipients. These findings align with the established hematologic toxicity profile of CDK4/6 inhibitors and previous real-world studies in older patients [4–6]. Recent meta-analyses further emphasize the need to balance efficacy against hematologic toxicity and potential dose modifications [15,16]. Anemia and thrombocytopenia were numerically more frequent with CDK4/6i + AI, but the differences were not statistically significant.

Among nonhematologic adverse events, gastrointestinal, cardiac, hepatic, dermatologic, and pulmonary toxicities did not differ significantly between groups. Renal adverse events were more frequent with CDK4/6i + AI (12.5% vs. 0%; $p = 0.008$), whereas neuromusculoskeletal toxicity was more frequent in the comparator group (5.9% vs. 17.8%; $p = 0.029$). These renal findings warrant cautious interpretation. A systematic review and meta-analysis reported increased renal adverse events with CDK4/6 inhibitors [19]. However, inhibition of renal tubular creatinine transport may cause serum creatinine elevations without actual impairment of kidney function, a phenomenon known as pseudo-acute kidney injury [20]. As renal events were retrospectively identified, isolated creatinine elevations could not be reliably distinguished from confirmed kidney injury. Thus, the observed difference should not be interpreted as an increased incidence of confirmed acute kidney injury. Similarly, higher neuromusculoskeletal toxicity in the comparator group may reflect treatment heterogeneity, baseline functional differences, or documentation practices rather than a direct treatment effect.

Several additional considerations limit the interpretation of the safety findings. The comparator group combined endocrine monotherapy, chemotherapy, and CDK4/6 inhibitor plus fulvestrant, making agent-specific comparisons difficult. Adverse events were retrospectively identified from clinical and laboratory records, and mild or transient toxicities may have been incompletely captured. The absence of recorded toxicity does not necessarily establish that no adverse event occurred. Furthermore, treatment exposure duration, dose intensity, interruptions, and dose reductions were not incorporated into the comparative analyses. Since no adjustment for multiple testing was performed, the statistically significant differences observed for renal and neuromusculoskeletal toxicities should be

considered exploratory. Detailed prospective monitoring would be required to establish their clinical significance.

This study has several strengths. It included patients from 14 oncology centers across Türkiye and focused specifically on women aged 70 years and older with de novo HR+/HER2− metastatic breast cancer. The inclusion of treatment-selection models, primary and secondary survival comparisons, adjusted prognostic analyses, and adverse-event assessments allowed a comprehensive evaluation of routine clinical management. The restriction to de novo metastatic disease also reduced heterogeneity related to previous treatment for earlier-stage breast cancer.

Nevertheless, several important limitations should be acknowledged. First, the retrospective observational design introduces potential selection bias, information bias, and residual confounding. Second, the relatively small and heterogeneous comparator group limits the interpretation of treatment effectiveness and safety. Third, although multivariable models included relevant baseline characteristics, comprehensive geriatric assessments and validated frailty measures were not routinely performed or available across participating centers. Consequently, frailty could not be incorporated into the adjusted analyses, and residual confounding related to geriatric vulnerability cannot be excluded. Information on comorbidity severity, socioeconomic factors, patient preferences, and treatment access was also unavailable. Fourth, information regarding locoregional treatments, including surgery, radiotherapy, and other local interventions, and their timing relative to first-line systemic therapy was not systematically collected. Therefore, these treatments could not be incorporated into the multivariable survival models or evaluated through sensitivity analyses. Because patients selected for local treatment may differ in performance status, disease burden, and underlying tumor biology, unmeasured differences in local treatment exposure may have introduced additional selection bias and residual confounding, potentially leading to an overestimation of the observed associations between systemic treatment and survival. Fifth, the limited number of deaths and follow-up duration may have reduced the statistical power and precision of OS analyses. Sixth, although adverse events were graded according to CTCAE v5.0, disease progression and treatment-related adverse events were retrospectively assessed using routine medical records rather than standardized prospective evaluations. Differences in the completeness of adverse event documentation across participating centers cannot be excluded. In particular, recorded renal adverse events could not be reliably differentiated into isolated serum creatinine elevations and clinically confirmed kidney injury. Seventh, although dose reductions, treatment discontinuations, and subsequent-line treatments were recorded and descriptively reported, detailed treatment exposure, relative dose intensity, and the potential effects of treatment modifications and subsequent therapies on survival were not evaluated. Information regarding specific causes of death was also limited. Outcomes were not separately evaluated according to the individual CDK4/6 inhibitor administered. Eighth, molecular testing was incomplete, and the small number of documented alterations limited molecular subgroup analyses. Finally, secondary survival comparisons and exploratory safety analyses were not adjusted for multiple testing. The Cox regression findings should also be interpreted cautiously, as formal results of proportional hazards assumption testing were not reported.

5. Conclusions

In this multicenter real-world study, first-line CDK4/6i + AI therapy was associated with significantly longer PFS, but not OS, in women aged ≥ 70 years with de novo HR+/HER2− metastatic breast cancer. Treatment selection was associated with functional status and cardiac function, while increasing age predicted poorer survival. Neutropenia was the most frequently reported adverse event, whereas differences in renal and neuromus-

culoskeletal toxicities warrant further investigation. These findings support individualized treatment decisions beyond chronological age and highlight the need for prospective studies incorporating comprehensive geriatric assessment.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/jcm15228979/s1. Supplementary Table S1. Univariable and multivariable Cox proportional hazards regression analyses for overall and progression-free survival: CDK4/6i plus AI versus AI monotherapy.

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Data Availability Statement: The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request, subject to applicable ethical and institutional restrictions.

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