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ORIGINAL RESEARCH

Healthcare Resource Utilization and Cost Comparison Between Palbociclib, Abemaciclib, and Ribociclib Among Patients with HR+/HER2− Metastatic Breast Cancer

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Purpose: To evaluate economic outcomes in patients with hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2−) metastatic breast cancer (mBC) treated with a first- or second-line cyclin-dependent kinase 4/6 inhibitor (CDK4/6i).

Methods: This retrospective analysis utilized Optum's Clinformatics DataMart (January 1, 2014–September 30, 2021). Included patients had ≥1 pharmacy claim for palbociclib, abemaciclib, or ribociclib in first or second-line and ≥6 months of continuous health plan enrollment in preindex (index: date of first CDK4/6i claim) and follow-up periods. Mean all-cause per patient per month (PPPM) medical, healthcare resource utilization (HCRU) and costs, and outpatient pharmacy prescriptions costs were compared among CDK4/6is using stabilized inverse probability of treatment weighting (sIPTW).

Results: We identified 3,182 patients taking palbociclib, 286 taking abemaciclib, and 149 taking ribociclib, with median follow-ups of 20.8, 16.6, and 19.9 months, respectively. After sIPTW, palbociclib was associated with a lower risk of inpatient (IP) admissions versus abemaciclib (35.8% vs 41.6%; odds ratio: 1.31; P=0.034). No other significant differences were seen for HCRU. PPPM outpatient costs were significantly lower with palbociclib versus abemaciclib ($754; P=0.05). PPPM IP ($2,252 vs $6,286), medical ($6,948 vs $11,717), and total ($19,370 vs $23,639) costs were also lower with palbociclib versus abemaciclib, although not significant. There were no significant differences in PPPM HCRU or costs between palbociclib and ribociclib. In patients with Medicare, PPPM total medical costs were lower with palbociclib versus abemaciclib by $1,608 ($P$=0.04), while other costs were not significantly different. No significant differences in costs were seen with palbociclib versus ribociclib.

Conclusion: All-cause HCRU and costs were generally not different between the CDK4/6is but favored palbociclib for medical (including IP) costs versus abemaciclib. Due to limited patient numbers, uncertainty exists about abemaciclib and ribociclib cost estimations. Further studies of HCRU and costs are needed to support a cost-minimizing strategy for mBC.

Keywords: healthcare resource utilization, healthcare economics, CDK 4/6 inhibitors, HR+/HER2− metastatic breast cancer

Introduction

In 2023, an estimated 300,590 people were diagnosed with and 43,700 died from breast cancer (BC) in the United States (US).[1] Furthermore, 6%–10% of new cases are metastatic BC (mBC), and 20%–30% of patients with early-stage BC will eventually progress to mBC.[2] Approximately 4% of women with a history of BC are living with metastatic disease, for whom the 5-year survival rate is less than 30%.[3] The cost of treating mBC is substantial[4] and is projected to increase from $75 billion in 2020 to $152.4 billion by 2030 owing to an increase in patient numbers.[5]

The majority of patients with mBC have the hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2−) subtype;[3] guidelines recommend treating these patients with a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) in

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combination with endocrine therapy.[6] Three CDK4/6is have been approved by the US Food and Drug Administration[7–9] based on positive results from Phase 3 clinical trials, which reported progression-free survival (PFS) benefits with CDK4/6i treatment versus standard of care, with manageable tolerability profiles[10–16] and maintaining patient quality of life (QoL).[17–22] To date, no head-to-head randomized controlled trials have compared different CDK4/6is; however, indirect treatment comparisons[23,24] and real-world evidence comparisons[25,26] suggest no difference in efficacy, but differing safety profiles[27,28] and impacts on health-related QoL.[29] It is less clear how different CDK4/6is impact the economic burden of HR+/HER2– mBC.

Given the significant economic burden of mBC, healthcare providers and decision makers should consider healthcare resource utilization (HCRU) and costs alongside the efficacy and safety of proposed interventions. However, HCRU and cost data are usually not collected in clinical trials, and few studies evaluate these outcomes for CDK4/6i use in clinical practice. A recent article by Burne et al used data from the MarketScan Commercial and Medicare Supplemental database to compare HCRU and healthcare costs across all 3 CDK4/6is.[30] Total healthcare costs, medical costs, and pharmacy costs were significantly lower with ribociclib versus abemaciclib, but similar to palbociclib. Although this study provides insights into HCRU and costs associated with CDK4/6i use, it does have important limitations, particularly with its short treatment period (driven by a high prevalence of patients with later-line therapies) that may restrict its generalizability. To better inform decision makers, studies are needed to better understand HCRU and costs during a longer treatment period associated with current CDK4/6i standard of care use in the first and second lines.

There is further value in understanding which types of HCRU and costs are most important and how these change over the phases of care: from the initial period when treatment is started to the continuation of treatment, and finally the last period before treatment discontinuation, particularly if differential CDK4/6i toxicity profiles may be driving cost variations. As most patients with HR+/HER2– mBC are aged ≥ 65 years and typically have complex needs (eg, because of comorbidity burden), it is important to evaluate HCRU and costs in these patients as well.

To address these evidence gaps, the aim of our study was to assess all-cause HCRU and costs among adult patients with HR+/HER2– mBC who received a CDK4/6i in the first or second line over a period that captures the full course of treatment in real-world clinical practice. The study used administrative claims data from Optum Clinformatics DataMart (CDM), which contains a large commercial and Medicare-insured population.

Methods

Data Source

This study was conducted using Optum CDM standard view with mortality plus race and ethnicity data from January 1, 2014 to September 30, 2021. This database has been used previously to conduct similar studies.[31–34] Optum has administrative health insurance claims for members with medical and pharmacy coverage enrolled in commercial and Medicare Advantage health plans across all 50 states in the US. Longitudinal patient-level information is available on health plan enrollment, demographics, HCRU across different medical settings, and medication use. Optum data are deidentified and comply with the 1996 health Insurance Portability and Accountability Act.[31–34]

Study Design

This was an observational retrospective cohort study of patients identified from February 3, 2015 (date of first CDK4/6i treatment approval) to September 30, 2020 (Supplementary Figure S1). The study index date was defined as the date of the first observed claim for a CDK4/6i prescription during the patient selection window. The preindex period consisted of a 6-month period prior to the index date, and the follow-up period extended from the index date until the end of health or drug plan enrollment, death, or the end of study period. For the evaluation of study outcomes, all patients were followed from the study index date through discontinuation of CDK4/6i, disenrollment from health or drug plan, or the end of study period, whichever occurred first.

Sample Selection

Adult patients with HR+/HER2– mBC with ≥ 1 prescription claim for CDK4/6i therapy in the first- or second-line setting were included (Figure 1). Patients with mBC were classified as having de novo mBC if they had evidence of secondary

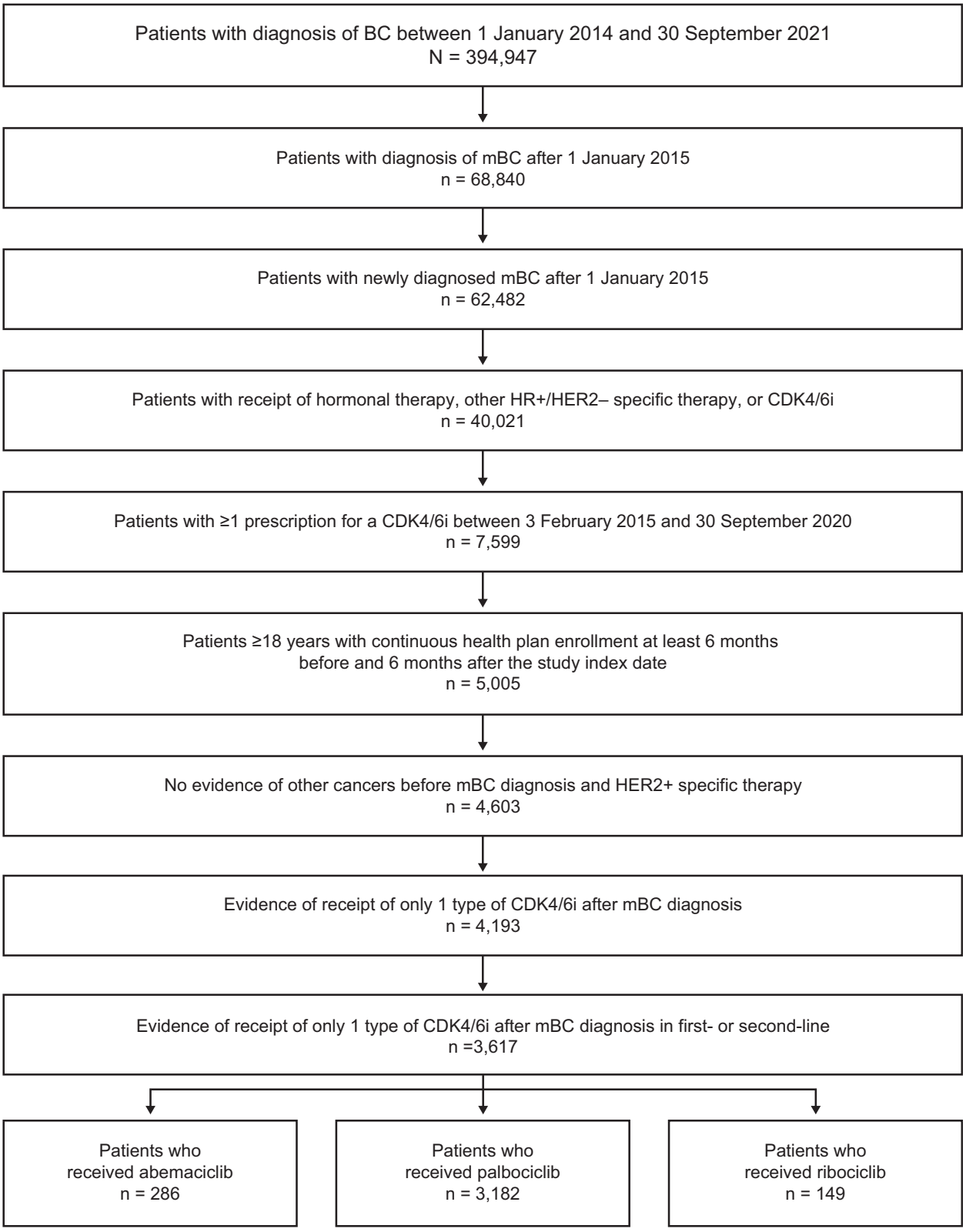

Figure 1 Patient identification flowchart.
Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; HER2–, human epidermal receptor 2-negative; HER2+, human epidermal receptor 2-positive; HR+, hormone receptor positive; mBC, metastatic breast cancer.

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malignancy within a 60-day period before or after the first medical encounter with a diagnosis of BC. Patients with evidence of secondary malignancy more than 60 days after the first medical encounter with a diagnosis of BC were classified as patients who progressed or recurred to mBC. Consistent with previous studies,[30,35] HR+/HER2– status of patients was based on an observed claim for hormonal therapy or other therapy (ie, everolimus, olaparib, talazoparib) directed toward HR+/HER2–BC, or CDK4/6i and no receipt of any treatment indicated for HER2+ BC, any time after first evidence of BC.

Patients were required to have ≥ 6 months of continuous health plan enrollment in the preindex and follow-up periods,[36] except for patients who died within the first 6 months after the study index date. Patients were excluded if they had evidence of cancers other than BC in the preindex period or were treated with multiple CDK4/6is during the follow-up period. Following identification of the study population, patients were categorized into 3 mutually exclusive cohorts based on the CDK4/6i they received on the index date: abemaciclib, ribociclib, or palbociclib.

Study Outcomes

Patient characteristics were assessed in the 6-month preindex period or at the study index date. Patient characteristics assessed included: age, gender, race, region, health plan type (commercial and Medicare), year of mBC diagnosis and initiation of CDK4/6i, National Cancer Institute's Comorbidity Index (NCICI),[37] type of mBC diagnosis (de novo or recurrent), and organ-level metastatic site.

HCRU and costs were assessed separately for each CDK4/6i cohort in aggregate and by care setting/resource. Per-patient-per-month (PPPM) HCRU and costs during CDK4/6i therapy were calculated by dividing the number of times the resource was utilized and the costs incurred by the total duration of CDK4/6i-based therapy. HCRU included all healthcare claims (inpatient [IP] admissions, total hospital days, emergency department [ED] visits, office visits, outpatient hospital, urgent care, outpatient pharmacy claims, and other outpatient/ancillary care) regardless of the diagnoses and procedures. Utilization of electrocardiogram (ECG) was also assessed. HCRU for IPs, total hospital days, hospital outpatient visits, and ED visits are only reported for patients who had ≥ 1 such visit. Healthcare costs were assessed from a payer perspective and included the estimated allowed amounts reported for each claim. Total medical costs for each patient comprised patient-level IP costs, ED costs, and all outpatient costs. Outpatient pharmacy costs were based on wholesale acquisition costs for CDK4/6i and endocrine partner, including dose adjustments and wastage.

A phase of care approach to assess costs during the initial (maximum of 3 months after initiation of CDK4/6i-based treatment), continuing (time period between initial period and terminal/discontinuation period), and final (maximum of 3 months before death or CDK4/6i-based treatment discontinuation) time periods, respectively, was used (Supplementary Figure S2), similar to that typically used to estimate direct medical costs among patients with cancer.[38] A subgroup analysis restricted to patients aged ≥ 65 years enrolled in Medicare Advantage was conducted. All costs were converted to 2021 US dollars using the medical care component of the US Consumer Price Index.

Statistical Analysis

All study measures were summarized descriptively. Propensity score-based stabilized inverse probability treatment weighting (sIPTW) was used to balance cohort baseline characteristics. The multinomial logistic regression model included patient demographics (age at index, gender, race, and health plan type) and clinical characteristics (de novo mBC, bone-only disease at index treatment, brain/CNS metastasis at index treatment, visceral disease at index treatment, and NCICI score) that may influence the choice of treatment as independent variables. Similar to Burne et al,[30] year of mBC diagnosis and CDK4/6i treatment start were not corrected for, as this would reduce sample size significantly due to the large imbalance in year of treatment introduction between the CDK4/6is and downweigh patients who were treated with palbociclib in the years 2015 and 2016. In line with Burne et al, baseline HCRU and costs were also not adjusted for; however, adjustment of other baseline characteristics such as age, would reduce potential cost differences at baseline between the treatments. Individual propensity score derived via multinomial logistic regression was used to compute individual sIPTW. A threshold for the standardized mean difference (SMD) of < 0.10 was used to indicate balanced cohorts. Factors with SMD of ≥ 0.10 were adjusted again in the outcome assessment regressions.

Regression analyses with sIPTW were used to compare HCRU and costs during the follow-up period. Logistic regression was used to evaluate the association between cohorts and HCRU. Incidence rate ratios (IRRs) for HCRU

count outcomes were calculated using negative binomial regression. Generalized linear models with a log link function and gamma distribution for the error term were used for cost outcomes.[39] Two-part models were used for predicting IP, ED, and outpatient costs. All models considered the palbociclib cohort as the reference category and were run separately for the overall population and ≥ 65 years of age subgroup. Comparative results are reported with *P* values, where $P \leq 0.05$ was considered statistically significant.

Results

The final analytical sample included 3,617 patients who received first- or second-line CDK4/6i treatment (3,182 palbociclib [88%], 286 abemaciclib [8%], and 149 ribociclib [4%]) (Figure 1). A total of 179 patients with use of multiple CDK4/6is observed during the study follow-up were excluded. The median duration of follow-up for the palbociclib, abemaciclib, ribociclib cohorts was 20.8 (range: 0.3–79.4), 16.6 (range: 0.03–46.3), and 19.9 months (range: 0.9–52.9), respectively. Approximately 60% of patients received first-line CDK4/6i treatment (palbociclib: 64%; abemaciclib: 57%; ribociclib: 62%) and the remainder in the second line. The median time of initiation of index CDK4/6i from mBC diagnosis was 1.3 months for palbociclib, 2.1 months for abemaciclib, and 2.4 months for ribociclib. The Kaplan–Meier estimated median time to treatment discontinuation was 16.7 months (95% CI: 13.2–19.6) for abemaciclib, 16.1 months (95% CI: 15.0–17.1) for palbociclib, and 14.4 months (95% CI: 11.0–18.0) for ribociclib.

Demographics and Clinical Characteristics

Unadjusted and sIPTW-adjusted baseline demographic and clinical characteristics are presented in Table 1. Median age ranged from 69.0–71.0 years, with 62.9%–74.5% of patients aged ≥ 65 years, and 65.4%–77.2% enrolled in Medicare. Approximately half of patients had de novo mBC, 36.5%–40.3% had visceral metastases, 27.6%–32.2% had bone-only metastases, and 5.4%–14.3% had brain/CNS metastases. Patient comorbidity burden was high, with an unadjusted NCICI ≥ 2 score ranging from 41.6%–48.3%. Of the patients enrolled in Medicare, 29.7% were enrolled in a health maintenance organization (HMO), 8.7% were enrolled in preferred provider organizations (PPOs), and 61.6% in others. Among commercially enrolled patients, 72.8% were enrolled in point-of-service, 13.3% in HMOs, 10.4% in exclusive provider organizations, 1.8% in indemnity plans, 1.3% in PPOs, and 0.5% in others.

Before sIPTW, relative to the palbociclib cohort, the abemaciclib cohort included fewer patients aged 75–84 years (18.9% vs 24.7%, SMD = 0.14), fewer White (64.7% vs 69.7%, SMD = 0.11) and Hispanic patients (5.6% vs 9.2%, SMD = 0.14), more Asian patients (4.9% vs 3.0%, SMD = 0.10), fewer patients with bone-only metastases (27.6% vs 32.2%, SMD = 0.10), and more patients with brain metastases (14.3% vs 6.3%, SMD = 0.27).

Before sIPTW, relative to the palbociclib cohort, the ribociclib cohort had fewer patients aged 55–64 years (14.1% vs 20.8%, SMD = 0.18), more patients aged 65–74 years (39.6% vs 34.7%, SMD = 0.10) and 75–84 years (29.5% vs 24.7%, SMD = 0.11), more patients enrolled in Medicare (77.2% vs 67.0%, SMD = 0.23), fewer White patients (60.4% vs 69.7%, SMD = 0.20), more patients with de novo mBC (52.4% vs 46.9%, SMD = 0.11), and fewer patients with a NCICI score < 1 (31.5% vs 36.6%, SMD = 0.11) but more with a score > 2 (48.3% vs 41.8%, SMD = 0.13). After sIPTW adjustment, demographic and clinical characteristics of the 3 cohorts were well balanced (SMD < 0.10), and a double adjustment in regression was not needed. After sIPTW adjustment the median PPPM baseline costs were not different; $4,475 for ribociclib, $4,631 for palbociclib, and $4,928 for abemaciclib (absolute SMD: palbociclib vs ribociclib, 0.04; palbociclib vs abemaciclib, 0.09).

HCRU

During treatment, over a third of patients had an IP. The proportion of these patients was significantly higher with abemaciclib versus palbociclib (41.6% vs 35.8%; odds ratio: 1.31; $P = 0.03$). In addition, mean number of PPPM IPs were highest in the abemaciclib cohort (0.50), followed by the palbociclib (0.31) and ribociclib (0.28) cohorts (Table 2 and Supplementary Figure S3), with the estimated IRR trending toward being higher with abemaciclib versus palbociclib, but was not statistically significant (IRR: 1.32, $P = 0.06$).

Mean PPPM number of hospital days was highest with abemaciclib (2.85 days), followed by palbociclib (2.26 days) then ribociclib (2.24 days), and the estimated IRR trended toward a higher number with abemaciclib versus palbociclib,

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Table 1 Baseline Demographic and Clinical Characteristics of Patients with mBC Receiving First- or Second-Line Treatment with a CDK4/6i Before and After sIPTW Adjustment

	Before sIPTW					After sIPTW				
	Palbociclib (N = 3,182)	Abemaciclib (N = 286)		Ribociclib (N = 149)		Palbociclib (N = 3,182)	Abemaciclib (N = 286)		Ribociclib (N = 149)	
			Absolute SMD (vs palbociclib)		Absolute SMD (vs palbociclib)			Absolute SMD (vs palbociclib)		Absolute SMD (vs palbociclib)
Age										
Mean (SD)	67.8 (11.64)	66.8 (12.25)		69.6 (10.94)		67.81 (11.62)	67.8 (12.18)		68.5 (11.3)	
Median	69.0	69.0		71.0		69.0	70.0		70.0	
Age, years (n, %)										
18–54	436 (13.7)	44 (15.4)	0.05	17 (11.4)	0.07	437 (13.7)	40 (14.1)	0.01	19 (13.1)	0.02
55–64	661 (20.8)	62 (21.7)	0.02	21 (14.1)	0.18	655 (20.6)	60 (20.9)	0.01	30 (20.5)	0.00
65–74	1103 (34.7)	109 (38.1)	0.07	59 (39.6)	0.10	1118 (35.1)	97 (34.2)	0.02	52 (34.8)	0.01
75–84	785 (24.7)	54 (18.9)	0.14	44 (29.5)	0.11	777 (24.4)	71 (24.8)	0.01	37 (24.7)	0.01
≥ 85	197 (6.2)	17 (5.9)	0.01	8 (5.4)	0.04	195 (6.1)	17 (6.0)	0.01	10 (7.0)	0.03
Gender (n, %)			0.05		0.07			0.04		0.02
Female	3143 (98.8)	284 (99.3)		146 (98.0)		3143 (98.8)	283 (99.2)		146 (98.6)	
Male	38 (1.2)	2 (0.7)		3 (2.0)		38 (1.2)	2 (0.8)		2 (1.4)	
Unknown	1 (0.0)	0 (0.0)		0 (0.0)		1 (0.0)	0 (0.0)		0 (0.0)	
Race or Ethnicity										
African American	396 (12.5)	44 (15.4)	0.09	21 (14.1)	0.05	406 (12.8)	39 (13.6)	0.03	20 (13.7)	0.03
Asian	95 (3.0)	14 (4.9)	0.10	5 (3.4)	0.02	100 (3.2)	9 (3.2)	0.00	3 (2.2)	0.06
Caucasian	2217 (69.7)	185 (64.7)	0.11	90 (60.4)	0.20	2192 (68.9)	197 (69)	0.00	100 (67.2)	0.04
Hispanic	292 (9.2)	16 (5.6)	0.14	18 (12.1)	0.09	287 (9.0)	24 (8.5)	0.02	16 (10.6)	0.05
Unknown	182 (5.7)	27 (9.4)	0.14	15 (10.1)	0.16	197 (6.2)	16 (5.7)	0.02	9 (6.3)	0.00
Region (n, %)										
Northeast	338 (10.6)	26 (9.1)	0.05	10 (6.7)	0.14	329 (10.3)	30 (10.7)	0.01	14 (9.3)	0.04
Midwest/North Central	701 (22.0)	49 (17.1)	0.12	32 (21.5)	0.01	688 (21.6)	59 (20.6)	0.02	32 (21.3)	0.01
South	1370 (43.1)	156 (54.6)	0.23	67 (45.0)	0.03	1401 (44)	125 (43.7)	0.01	67 (45.2)	0.02
West	765 (24.0)	54 (18.9)	0.13	40 (26.9)	0.06	756 (23.8)	71 (24.8)	0.03	36 (24.3)	0.01
Missing/unknown	8 (0.3)	1 (0.4)		0 (0.0)		8 (0.3)	0 (0.1)		0 (0.0)	
Health plan type (n, %)			0.03		0.23			0.01		0.02
Commercial	1049 (33.0)	99 (34.6)		34 (22.8)		1040 (32.7)	95 (33.2)		47 (31.7)	
Medicare	2133 (67.0)	187 (65.4)		115 (77.2)		2142 (67.3)	191 (66.8)		101 (68.3)	

De novo mBC diagnosis (n, %)	1492 (46.9)	144 (50.4)	0.07	78 (52.4)	0.11	1508 (47.4)	139 (48.7)	0.03	70 (47.0)	0.01
Recurrent mBC (n, %)	1690 (53.1)	142 (49.7)		71 (47.7)		1674 (52.6)	146 (51.3)		79 (53.0)	
Metastatic site(s) (n, %)[a]										
Bone-only disease	1024 (32.2)	79 (27.6)	0.10	47 (31.5)	0.01	1011 (31.8)	85 (30.0)	0.04	44 (29.5)	0.05
Brain/CNS metastasis	200 (6.3)	41 (14.3)	0.27	8 (5.4)	0.04	219 (6.9)	20 (7.1)	0.01	13 (8.7)	0.07
Visceral disease	1161 (36.5)	115 (40.2)	0.08	60 (40.3)	0.08	1176 (37.0)	110 (38.6)	0.03	55 (37.0)	0.00
NCICI score (n, %)										
< 1	1166 (36.6)	100 (35.0)	0.04	47 (31.5)	0.11	1155 (36.3)	101 (35.6)	0.01	54 (36.5)	0.00
1–2	685 (21.5)	67 (23.4)	0.05	30 (20.1)	0.03	688 (21.6)	62 (21.7)	0.00	31 (21.0)	0.01
> 2	1331 (41.8)	119 (41.6)	0.00	72 (48.3)	0.13	1339 (42.1)	122 (42.7)	0.01	63 (42.5)	0.01
Year of mBC diagnosis (n, %)										
2015	495 (15.6)	11 (3.9)		4 (2.7)		493 (15.5)	13 (4.4)		4 (3.0)	
2016	611 (19.2)	14 (4.9)		10 (6.7)		614 (19.3)	16 (5.4)		8 (5.6)	
2017	663 (20.8)	43 (15.0)		50 (33.6)		663 (20.8)	39 (13.7)		55 (37.0)	
2018	580 (18.2)	74 (25.9)		34 (22.8)		581 (18.2)	75 (26.3)		33 (22.4)	
2019	583 (18.3)	91 (31.8)		35 (23.5)		583 (18.3)	86 (30.3)		35 (23.5)	
2020	250 (7.9)	53 (18.5)		16 (10.7)		249 (7.8)	57 (19.9)		12 (8.4)	
Year of CDK4/6 initiation (n, %)										
2015	235 (7.4)	0 (0)		0 (0)		233 (7.3)	0 (0)		0 (0)	
2016	516 (16.2)	0 (0)		0 (0)		517 (16.2)	0 (0)		0 (0)	
2017	700 (22)	12 (4.2)		34 (22.8)		701 (22.0)	12 (4.2)		37 (24.7)	
2018	577 (18.1)	76 (26.6)		43 (28.9)		578 (18.2)	74 (26.0)		43 (28.9)	
2019	703 (22.1)	109 (38.1)		38 (25.5)		702 (22.1)	104 (36.6)		40 (26.9)	
2020	451 (14.2)	89 (31.1)		34 (22.8)		451 (14.2)	95 (33.2)		29 (19.5)	

Notes: [a]mBC metastasis at the study index date was assessed using ICD-9-CM and ICD-10-CM codes (Supplementary Table S1).

Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CNS, central nervous system; ICD-9/10-CM, International Classification of Disease, Ninth/Tenth Revision, Clinical Modification; mBC, metastatic breast cancer; NCICI, National Cancer Institute's Comorbidity Index; SD, standard deviation; sIPTW, stabilized inverse probability treatment weighting; SMD, standardized mean difference.

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Table 2 All-Cause HCRU and Costs Among Patients Receiving a CDK4/6i After sIPTW Adjustment, from Index Date to Treatment Discontinuation in Total Population and in Patients Aged ≥ 65 Years Enrolled in Medicare Advantage

	Palbociclib		Abemaciclib		Ribociclib		Abemaciclib vs Palbociclib		Ribociclib vs Palbociclib	
							OR/ IRR/ Incremental cost (95% CI)	*P* value	OR/ IRR/ Incremental cost (95% CI)	*P* value
All patients (n, %)	3,182	100.00%	286	100.00%	149	100.00%				
HCRU							**OR**		**OR**	
Any IP admission (n, %)	1140	35.8%	119	41.6%	53	35.6%	1.31 (1.02, 1.67)	0.03	1.10 (0.79, 1.55)	0.58
Any ED visit (n, %)	1148	36.1%	105	36.7%	54	36.2%	0.98 (0.76, 1.27)	0.90	1.09 (0.78, 1.53)	0.61
Any hospital outpatient visit (n, %)	2806	88.2%	256	89.5%	135	90.6%	1.06 (0.72, 1.56)	0.76	1.54 (0.84, 2.81)	0.16
Any office visit (n, %)	2912	91.5%	266	93.0%	136	91.3%	1.27 (0.79, 2.05)	0.32	1.15 (0.62, 2.14)	0.67
Any prescription (n, %)	3182	100.0%	286	100.0%	149	100.0%				
							IRR		**IRR**	
Number of IP admissions (PPPM, mean ± SD)	0.31	± 0.47	0.50	± 1.40	0.28	± 0.29	1.32 (0.99, 1.75)	0.06	1.08 (0.74, 1.58)	0.69
Number of hospital days (PPPM, mean ± SD)	2.26	± 4.63	2.85	± 5.18	2.24	± 2.84	1.43 (0.97, 2.11)	0.08	1.07 (0.64, 1.81)	0.80
Number of ED visits (PPPM, mean ± SD)	0.26	± 0.43	0.24	± 0.24	0.24	± 0.34	1.02 (0.79, 1.34)	0.86	0.94 (0.64, 1.36)	0.73
Number of hospital outpatient visits (PPPM, mean ± SD)	1.82	± 1.87	1.69	± 1.60	1.55	± 1.84	0.93 (0.81, 1.07)	0.29	0.87 (0.72, 1.06)	0.16
Number of office visits (PPPM, mean ± SD)	2.17	± 1.66	2.07	± 1.59	2.07	± 1.51	1.07 (0.96, 1.19)	0.23	1.01 (0.88, 1.17)	0.85
Number of prescriptions (PPPM, mean ± SD)	4.21	± 2.79	4.43	± 2.82	4.47	± 3.13	0.93 (0.87, 1.00)	0.07	1.00 (0.91, 1.10)	0.97
Healthcare costs ($)							**Incremental cost**		**Incremental cost**	
IP admission costs (PPPM, mean ± SD)	2252	± 9972	6286	± 52,557	4362	± 19,644	4034 (−1341, 9409)	0.14	2110 (−1311, 5530)	0.23
ED visit costs (PPPM, mean ± SD)	139	± 464	120	± 330	119	± 499	−19 (−58, 21)	0.35	−20 (−104, 65)	0.65
Outpatient visit costs (PPPM, mean ± SD)	4557	± 4919	5311	± 5842	3926	± 4174	754 (13, 1494)	0.05	−631 (−1311, 49)	0.07
Outpatient pharmacy costs (PPPM, mean ± SD)[a]	12,422	± 4750	11,921	± 8031	12,544	± 6595	−501 (−1468, 467)	0.31	122 (−1009, 1252)	0.83
Total medical costs (PPPM, mean ± SD)	6948	± 11,506	11,717	± 54,788	8407	± 20,027	4769 (−816 to 10,354)	0.09	1459 (−2126, 5044)	0.43
Total healthcare costs (PPPM, mean ± SD)	19,370	± 12,587	23,639	± 59,900	20,951	± 20,717	4268 (−1855 to 10,392)	0.17	1580 (−2096, 5257)	0.40
Utilization of ECG							**OR**		**OR**	
Any time during the follow-up (n, %)	1419	44.6%	139	48.6%	100	67.1%	1.16 (0.91, 1.48)	0.22	2.79 (1.96, 3.99)	<0.01
Initial phase (n, %)	674	21.2%	67	23.4%	78	52.4%	1.10 (0.83, 1.47)	0.51	4.52 (3.23, 6.31)	<0.01
Continuing phase (n, %)	833	36.9%	75	38.3%	42	40.8%	1.05 (0.80, 1.38)	0.73	1.12 (0.77, 1.61)	0.56
Terminal phase (n, %)	287	16.7%	25	20.7%	17	22.1%	0.93 (0.60, 1.44)	0.74	1.23 (0.72, 2.09)	0.44
Number of ECGs							**IRR**		**IRR**	
Any time during the follow-up (PPPM, mean ± SD)	0.18	± 0.64	0.31	± 1.11	0.32	± 0.61	1.34 (1.05, 1.72)	0.02	1.96 (1.43, 2.68)	<0.01
Initial phase (PPPM, mean ± SD)	0.19	± 0.69	0.30	± 1.14	0.54	± 0.80	1.26 (0.91, 1.75)	0.16	3.06 (2.06, 4.55)	<0.01
Continuing phase (PPPM, mean ± SD)	0.10	± 0.29	0.14	± 0.39	0.11	± 0.20	1.32 (0.98, 1.79)	0.07	1.19 (0.79, 1.77)	0.41
Terminal phase (PPPM, mean ± SD)	0.17	± 0.57	0.23	± 0.67	0.19	± 0.53	1.40 (0.80, 2.45)	0.24	1.27 (0.63, 2.56)	0.51

Patients aged ≥ 65 years and enrolled in Medicare Advantage (n, %)	1941	100.0%	173	100.0%	106	100.0%				
HCRU							**OR**		**OR**	
Any IP admission (n, %)	750	38.6%	75	43.4%	38	35.9%	1.28 (0.94, 1.76)	0.12	0.97 (0.62, 1.51)	0.90
Any ED visit (n, %)	657	33.9%	57	33.0%	31	29.3%	0.94 (0.67, 1.31)	0.70	0.79 (0.49, 1.27)	0.33
Any hospital outpatient visit (n, %)	1681	86.6%	152	87.9%	93	87.7%	1.08 (0.67, 1.74)	0.76	1.30 (0.66, 2.57)	0.45
Any office visit (n, %)	1716	88.4%	155	89.6%	95	89.6%	1.23 (0.72, 2.08)	0.45	1.28 (0.61, 2.68)	0.52
Any prescription (n, %)	1941	100.0%	173	100.0%	106	100.0%				
							IRR		**IRR**	
Number of IP admissions (PPPM, mean ± SD)	0.3	± 0.42	0.41	± 0.72	0.28	± 0.31	1.21 (0.86, 1.69)	0.28	1.10 (0.71, 1.72)	0.67
Number of hospital days (PPPM, mean ± SD)	2.4	± 4.79	3.02	± 5.53	2.4	± 2.75	1.30 (0.81, 2.08)	0.28	1.12 (0.60, 2.10)	0.72
Number of ED visits (PPPM, mean ± SD)	0.23	± 0.42	0.23	± 0.25	0.22	± 0.37	1.04 (0.74, 1.45)	0.82	0.84 (0.52, 1.34)	0.46
Number of hospital outpatient visits (PPPM, mean ± SD)	1.86	± 2.05	1.66	± 1.51	1.69	± 2.03	0.94 (0.78, 1.12)	0.47	0.97 (0.76, 1.24)	0.79
Number of office visits (PPPM, mean ± SD)	1.94	± 1.58	1.88	± 1.44	1.79	± 1.28	1.02 (0.88, 1.19)	0.78	0.94 (0.76, 1.15)	0.54
Number of prescriptions (PPPM, mean ± SD)	4.52	± 2.86	4.08	± 3.07	3.98	± 2.42	0.88 (0.81, 0.96)	<0.01	0.88 (0.76, 0.99)	0.03
Healthcare costs ($)							**Incremental cost**		**Incremental cost**	
IP admission costs (PPPM, mean ± SD)	2074	± 5849	3374	± 10,891	3620	± 20,580	1070 (−178, 2319)	0.09	1215 (−1652, 4082)	0.41
ED visit costs (PPPM, mean ± SD)	126	± 456	112	± 365	130	± 578	−19 (−69, 31)	0.46	−12 (−119, 94)	0.82
Outpatient visit costs (PPPM, mean ± SD)	4055	± 4708	4599	± 5296	3703	± 4602	572 (−321, 1464)	0.21	−322 (−1373, 730)	0.55
Outpatient pharmacy costs (PPPM, mean ± SD)[a]	11,937	± 5131	10,956	± 7475	10,643	± 5863	−921 (−2162, 320)	0.15	−1192 (−2575, 192)	0.09
Total medical costs (PPPM, mean ± SD)	6255	± 7927	8085	± 12,536	7452	± 20,937	1,608 (99, 3116)	0.04	1283 (−2392, 4957)	0.49
Total healthcare costs (PPPM, mean ± SD)	18,192	± 9314	19,040	± 14,669	18,095	± 21,710	952 (−1126, 3029)	0.37	411 (−3980, 4802)	0.85

Notes: [a]Wholesale acquisition costs for CDK4/6i accounting for dose adjustments and wastage.

Abbreviations: CDK4/6i, cyclin-dependent 4/6 inhibitor; CI, confidence interval; ECG, electrocardiogram; ED, emergency department; HCRU, healthcare resource utilization; IP, inpatient; IRR, incidence rate ratio; OR, odds ratio; PPPM, per patient per month; sIPTW, stabilized inverse probability treatment weighting; SD, standard deviation.

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although this was not statistically significant (IRR: 1.43, $P = 0.08$). Mean PPPM number of and proportion of patients with ED visits, office visits, and prescriptions were similar across all 3 CDK4/6i cohorts.

Patients in the ribociclib cohort had a higher rate of ECG utilization compared with palbociclib, while no statistically significant differences were observed for any other HCRU outcomes (Table 2 and Supplementary Figure S3).

Healthcare Costs

After sIPTW adjustment, mean PPPM total costs were lowest in the palbociclib cohort ($19,370), followed by the ribociclib cohort ($20,951), then the abemaciclib ($23,639) cohort (Table 2 and Figure 2). This resulted in monthly incremental, but not statistically significant, mean total healthcare costs of $4,268 PPPM ($P = 0.17$) with abemaciclib and $1,580 ($P = 0.40$) with ribociclib versus palbociclib. Numerically, medical costs were higher with abemaciclib ($11,717; incremental costs vs palbociclib: $4,769; $P = 0.09$) and ribociclib ($8,407; incremental costs vs palbociclib: $1,459; $P = 0.43$) versus palbociclib ($6,948), but not statistically significant (Table 2 and Figure 3). In turn, these costs were driven by numerically higher PPPM IP costs with abemaciclib ($6,286; incremental cost vs palbociclib: $4,034, $P = 0.14$) and ribociclib ($4,362; incremental cost vs palbociclib: $2,110; $P = 0.23$) versus palbociclib ($2,252), although differences were not statistically significant.

Mean PPPM outpatient visit costs were significantly higher with abemaciclib versus palbociclib (incremental cost: $754, $P = 0.05$) but not for ED visits (incremental cost: –$19, $P = 0.35$). No differences were observed between ribociclib and palbociclib for ED visits (incremental cost: –$20, $P = 0.65$) or outpatient visits (incremental cost: –$631, $P = 0.07$). Finally, outpatient pharmacy costs (including dose adjustments and wastage) were not different across the 3 cohorts, ranging from $11,921 with abemaciclib (incremental cost vs palbociclib: –$501; $P = 0.31$) to $12,544 with ribociclib (incremental cost vs palbociclib: $122, $P = 0.83$).

When considering phase of care, PPPM costs were highest during the initial phase, followed by the terminal/discontinuation phase and then the continuing phase (Figure 4). During the initial period, mean PPPM total medical costs were highest with abemaciclib ($13,425), followed by ribociclib ($9,638) and palbociclib ($7,869). Compared with palbociclib, incremental initial period costs were higher (borderline significant) for abemaciclib (incremental cost: $5,556 [95% CI: -$71 to $11,183], $P = 0.05$) and not statistically different for ribociclib (incremental cost: $1,769 [95% CI:

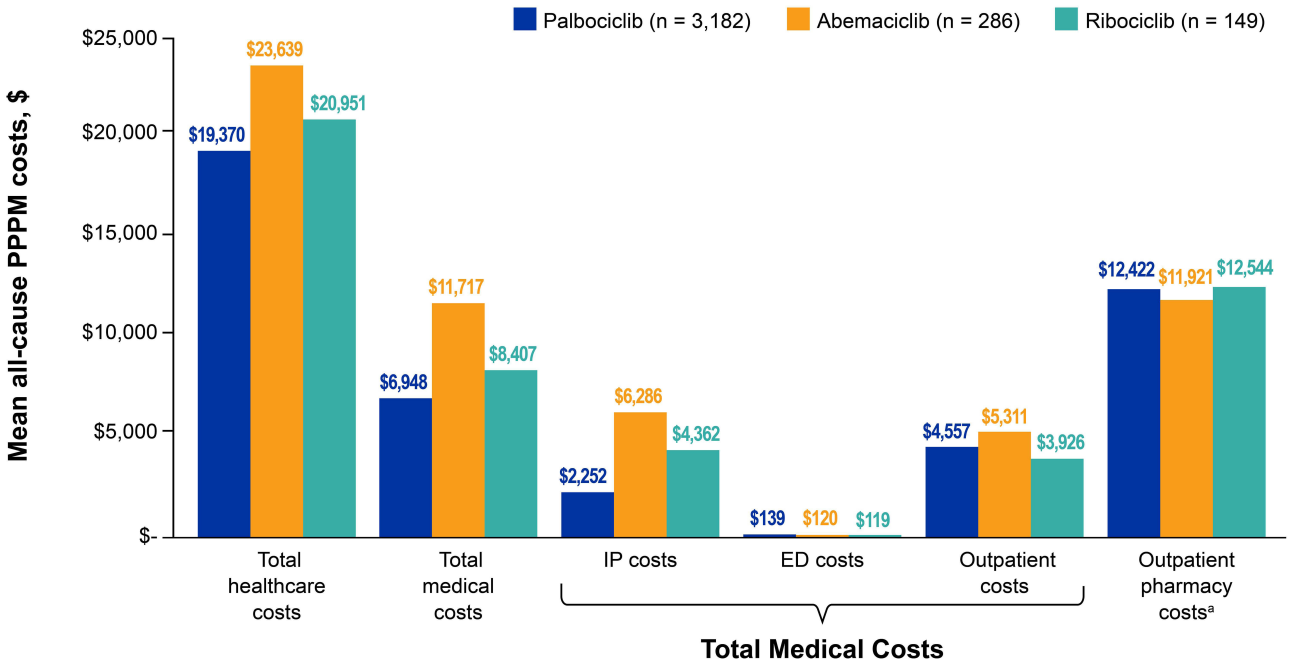

Figure 2 Mean all-cause PPPM costs in patients treated with palbociclib, abemaciclib, or ribociclib.
Notes: [a]Wholesale acquisition costs for CDK4/6i accounting for dose adjustments and wastage.
Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ED, emergency department; IP, inpatient; PPPM, per patient per month.

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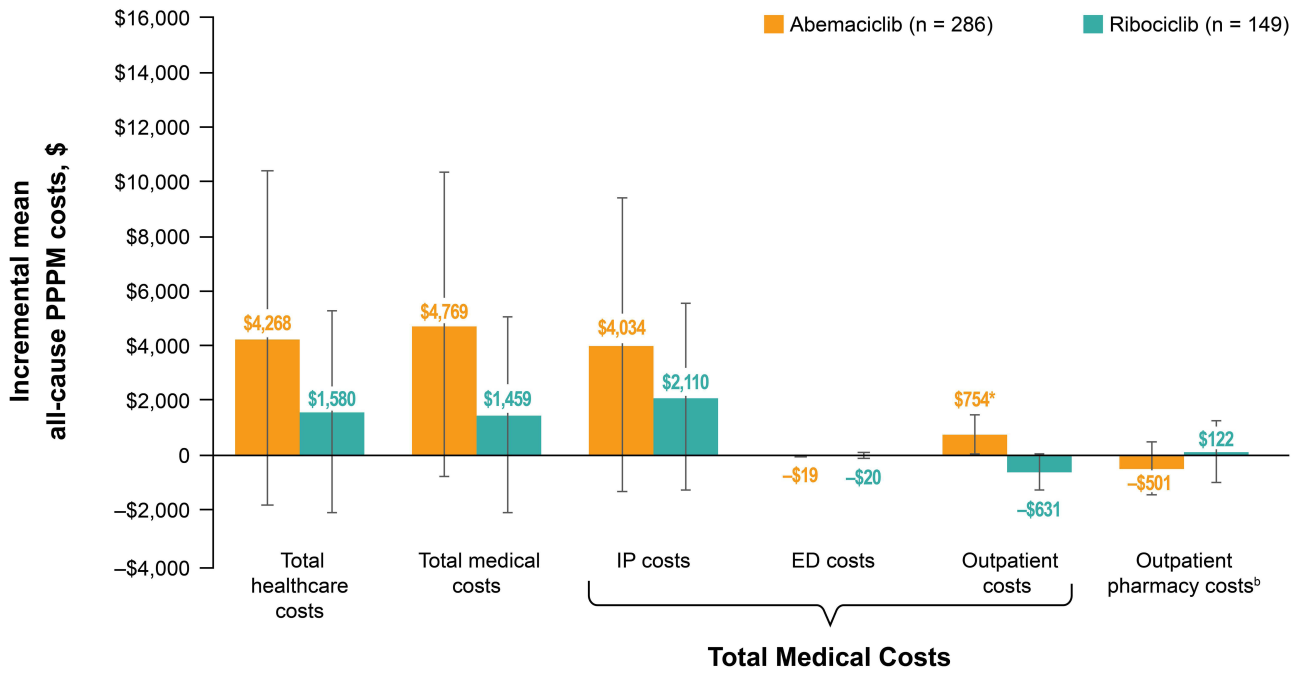

Figure 3 Incremental mean all-cause PPPM costs[a] in patients treated with abemaciclib or ribociclib compared with palbociclib.
Notes: [a]The incremental costs were computed using regression analysis, which adjusted for factors that remained imbalanced between the cohorts.[b]Wholesale acquisition costs for CDK4/6i, accounting for dose adjustments and wastage.*$P < 0.05$.
Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ED, emergency department; IP, inpatient; PPPM, per patient per month.

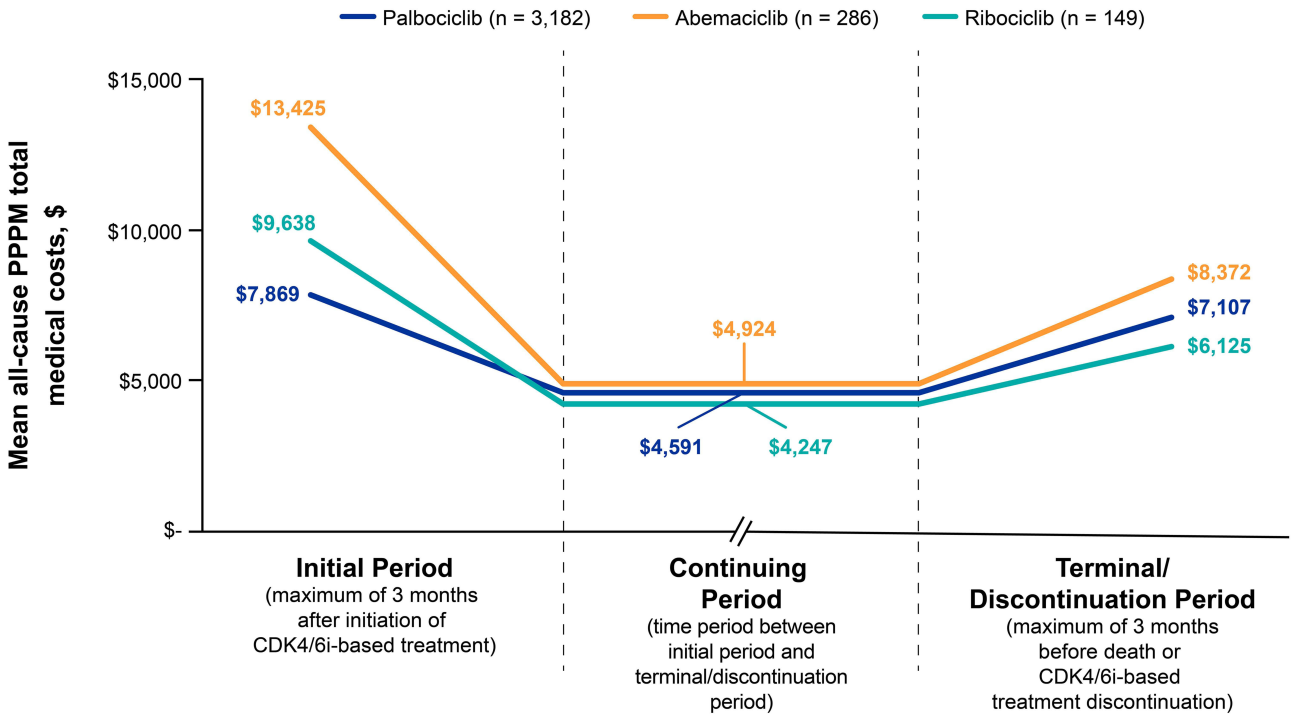

Figure 4 Mean all-cause PPPM total medical costs in patients treated with abemaciclib, ribociclib, or palbociclib, stratified by phase of care.
Notes: For patients with limited follow-up data (< 6 months), the initial phase was prioritized over the terminal phase.
Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; PPPM, per patient per month.

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-$2,602 to $6,139], P = 0.43). During the continuing phase, mean PPPM total medical costs were similar across all cohorts, $4,247 for ribociclib (incremental cost compared to palbociclib: $-345 [95% CI: -$1,422 to $733], P= 0.53), $4,591 for palbociclib, and $4,924 for abemaciclib (incremental cost compared to palbociclib: $332 [95% CI: -$545 to $1,209], P = 0.46). Finally, during the terminal/discontinuation phase, abemaciclib had the highest mean PPPM total medical costs ($8,372; incremental cost compared to palbociclib: $1,265 [95% CI: -$1,022 to $3,552], P = 0.28) followed by palbociclib ($7107) and ribociclib ($6,125; incremental cost compared to palbociclib: -$982 [95% CI: -$2,921 to $957], P = 0.32).

HCRU and Costs Among Patients Aged ≥65 years and Enrolled in Medicare Advantage

HCRU and costs between cohorts, for patients aged ≥65 years and enrolled in Medicare were similar to the total population (Table 2; Supplementary Figures S4 and S5). No statistically significant differences were observed between CDK4/6is for HCRU outcomes, except for the mean PPPM number of prescriptions, which was significantly lower with abemaciclib (4.08; IRR: 0.88; P < 0.01) and ribociclib (3.98; IRR: 0.88; P = 0.03) versus palbociclib (4.52).

Mean PPPM total medical costs were significantly higher with abemaciclib versus palbociclib ($8,085 vs $6,255; incremental cost: $1,608; P = 0.04), while total healthcare cost was not different ($19,040 vs $18,192; incremental cost: $952; P = 0.37). There were no differences in PPPM total medical costs ($7,452 vs $6,255; incremental cost: $1,283; P = 0.49), or total healthcare cost ($18,095 vs $18,192; incremental cost: $411; P = 0.85) with ribociclib compared to palbociclib. Finally, outpatient pharmacy costs were numerically lower, but not statistically significant, with abemaciclib ($10,956) and ribociclib ($10,643) compared with palbociclib ($11,937; incremental cost vs ribociclib: –$921, P = 0.15 and incremental cost vs ribociclib: –$1,192, P = 0.09).

Discussion

With a median follow-up of over 20 months, our study provides a unique real-world HCRU and cost comparison of alternative CDK4/6i choices in patients with HR+/HER2– mBC. To the best of our knowledge, our study is the first to assess HCRU and costs of these treatments in the US in the approved 1st and 2nd line mBC indications and spanning a normal treatment period with different phases of treatment. Other than IP admissions, which were 30% more likely for patients taking abemaciclib (compared with palbociclib), we found that all-cause HCRU was generally not significant across the 3 CDK4/6is. Furthermore, no significant differences in total costs between the treatments were found; however, compared with palbociclib, there were higher PPPM outpatient medical visit costs and a trend for higher total medical costs, driven primarily by higher IP costs with abemaciclib. In addition, there was a strong trend for higher medical costs during the initial 3-month treatment period with abemaciclib. No differences in costs were seen between palbociclib and ribociclib across cost categories. Similar results were seen in the subgroup of patients aged ≥ 65 years and enrolled in Medicare Advantage. However, the comparison between the treatments in our study is associated with uncertainty due to a low number of patients taking abemaciclib and ribociclib (12% in total), and in the population of 65 and older (13%).

Our results are in line with those of Burne et al,[30] in which higher total costs were seen with abemaciclib compared with palbociclib and ribociclib, but not between palbociclib and ribociclib. Although cost differences were not formally tested between abemaciclib and palbociclib in Burne et al,[30] mean adjusted PPPM total costs were found to be $6,634 higher with abemaciclib (ribociclib vs abemaciclib [–$7,886]) versus palbociclib, compared with $4,268 higher (not significant) in our study. In both studies, cost differences were primarily derived from total medical costs, driven in turn by IP and outpatient costs. Although both studies found no significant difference between palbociclib and ribociclib in total costs, some differences in the direction and magnitude of the incremental costs exist. In Burne et al,[30] mean PPPM total and medical cost were numerically lower with ribociclib compared with palbociclib ($859 and $841, respectively), while in our study, these costs were numerically higher ($1,580 and $1,459, respectively). IP costs were near identical between ribociclib and palbociclib in Burne et al[30] but $2,110 higher PPPM for ribociclib in our study. Contrary to Burne et al, who found significant outpatient PPPM cost savings with ribociclib versus palbociclib ($1,245), no significant difference was seen in our study.

Such variations may come down to differences in study design. First, our study was restricted to patients receiving CDK4/6is as first- or second-line treatment, more reflective of current clinical practice,[40,41] whereas almost half of

patients in Burne et al received a CDK4/6i in the third or later line. Second, mean treatment duration was considerably longer in our study than in Burne et al (17.5–24.4 vs 3.9–8.8 months, respectively).[30] Third, some parameters being weighted varied between studies, for example, menopausal status. Finally, patients in our study were considerably older than those in Burne et al (after reweighting: aged 69.0–70.0 years compared with 58.5–59.0 years, respectively); however, our median age is similar to that reported by SEER in which the median age for HR+/HER2– BC diagnosis was 64.0 years,[42] with nearly half [48.6%] of patients with HR+/HER2– "distant" BC aged ≥ 65.0 years. Thus, considering these points together, our study is arguably the more representative of current CDK4/6i standard of care for patients with HR+/HER2– mBC.

Our results highlight the importance of accounting for all costs of care, including medical and pharmacy costs, as differences between CDK4/6is may be more pronounced depending on what is being considered. For instance, total PPPM costs were $23,639 with abemaciclib and $19,360 with palbociclib, with higher medical costs ($11,717 vs $6,948) versus outpatient pharmacy costs ($11,921 vs $12,422) driving most of the total cost difference, whereas the drug costs were only $501 PPPM lower with abemaciclib than palbociclib. This effect was more evident in the subgroup of patients aged ≥ 65 years enrolled in Medicare, whereby outpatient pharmacy costs trended lower with abemaciclib and ribociclib compared with palbociclib, but total medical costs were higher (statistically significant with abemaciclib). This real-world finding that differences in medical costs can be higher or outweigh any drug cost differences has implications for cost-effectiveness modeling and result interpretation.

Our study highlights differences in costs during different phases of care over the course of treatment. For instance, mean PPPM medical costs during the first 3 months were highest with abemaciclib ($13,425), followed by ribociclib ($9,638) and palbociclib ($7,869). There was a strong trend (incremental cost: $5,556 [95% CI: -$71 to $11,183]; $P = 0.05$) in higher cost with abemaciclib versus palbociclib during this initial treatment period, but not for ribociclib. On the other hand, medical costs during the treatment period in between the first and last periods (ie, the continuing period) were lower compared with the initial period and not significant ($4,247–$4,924) across CDK4/6is. Finally, costs in the terminal/discontinuation period, while showing greater spread than the continuing period, were still not significantly different between the treatments (abemaciclib $8,372, palbociclib $7,107, and ribociclib $6,125).

There are several possible explanations for the medical cost differences between CDK4is and the cost patterns seen over time. CDK4/6is have different toxicity profiles,[27,28] which may have contributed to the differences between treatments during the first 3 months. Compared with palbociclib, an indirect treatment comparison shows that abemaciclib is more associated with diarrhea, vomiting, and infections, but less associated with neutropenia. Treatment of gastrointestinal toxicity and infections is more costly compared with CDK4/6i-induced neutropenia, which is primarily managed by dose adjustments and interruption. Patients taking abemaciclib were also more likely to discontinue treatment due to adverse events (AEs) compared with palbociclib.[27,28] In addition, an indirect comparison of patient-reported outcomes based on PALOMA 3 and MONARCH-2 found significantly different changes from baseline favoring palbociclib over abemaciclib in QoL, nausea/vomiting, appetite loss, diarrhea, and systemic therapy side effects.[29] Differences in AE profiles were also seen between ribociclib and palbociclib, with more vomiting and infections with ribociclib but less neutropenia; there were more discontinuations with ribociclib in the second line, but no difference in the first line.[27,28] Notably, in this study, AE costs were embedded in the aggregate medical costs of the Optum system and were not examined to identify HCRU and costs due to specific causes. Thus, future more detailed research is warranted to better understand the impact of the specific AE/tolerability profiles of CDK4/6is, particularly during the initial phase of treatment, on real-world HCRU and costs.

From the perspectives of payers and formulary decision-makers, our results indicate they should consider all types of healthcare costs as there may be differences across cost types, such as medical costs (likely explained in part by differences in tolerability), but not necessarily in overall costs. At this time, there is currently not enough information to prioritize between the CDK4/6i treatments from an overall cost perspective. Even from an effectiveness perspective, there is evidence to suggest that there may be no significant differences between the treatments in US clinical practice; a recently published (January 2025), large retrospective study using real-world data from the Flatiron Health electronic health record database (February 2015 through November 2023), reported that there were no significant differences in overall survival after sIPTW adjustment across >9,000 patients with HR+/HER2− mBC who were treated with first-line palbociclib, ribociclib, or abemaciclib in combination with an aromatase inhibitor, with similar findings observed across

older patient subgroups.[43] Taken together, all 3 agents may therefore provide the same pharmacoeconomic value. Nevertheless, given differences in tolerability profiles and monitoring requirements for these agents to accommodate the needs of comorbid and fragile patients with varying sensitivity to AEs (particularly in the Medicare eligible population treatments), the most conservative approach would be to have all 3 CDK4/6i options on the formulary. With continued emergence of real-world evidence on the comparative effectiveness of CDK4/6is, there are new opportunities for assessing their cost-effectiveness to more precisely determine their economic value and to help reduce the overall healthcare economic burden of mBC.

Study Limitations

This study is subject to the inherent limitations of using claims databases such as vulnerability to coding errors or underreporting of clinical conditions/events that do not trigger a billable event. Claims data reflect pharmacy fills of medication rather than actual use by patients. Treatments are not randomly assigned and therefore treatment selection may be confounded. Additionally, there is no information in claims data to directly identify mBC or HR+/ HER2– status; therefore, we used an algorithm based on treatments and procedures.[30]

Clinical characteristics not captured in the database, such as ECOG performance status or number of metastases, which may potentially affect CDK4/6i choice, could not be corrected by sIPTW. The year of initiation of CDK4/6i and baseline costs (which may include significant diagnostic costs) were not included as independent variables in the multinomial logistic regression computed to derive sIPTW weights. However, median PPPM total costs at baseline after sIPTW were almost identical between the treatments (a difference of less than $300; absolute SMD < 0.10) after sIPTW adjustment of other baseline characteristics. Patients with evidence of secondary malignancy within 60 days of initial BC diagnosis were considered to have de novo mBC, which may have resulted in misclassification of patients. However, such a criterion has been used previously,[44] and the treatment-based cohorts were balanced for de novo mBC status after sIPTW adjustment. Patient frailty was not assessed, although it is a strong predictor of treatment toxicity,[45] negatively impacts QoL,[46] and is associated with a higher risk of unfavorable discharge, prolonged hospital stay, and greater hospital costs.[47] Given the large proportion of frail patients with mBC,[47] understanding whether frailty contributes to differences seen among CDK4/6i medical costs, including the potential for channeling bias,[48] (drug tolerability driving prescription)[27] is important. Although comorbidities were assessed using the NCICI score, individual comorbidities that may drive costs were not assessed due to low patient numbers in the abemaciclib and ribociclib cohorts. Finally, reasons behind CDK4/6i choice are not recorded in the Optum claims data. However, biases due to differences over time in available CDK4/6 treatments may have affected the choice of treatment in our study, which could not be controlled for.

In our study, similar to Burne et al, the majority (88%) of the patients were treated with palbociclib and included a low number of patients treated with abemaciclib (286 vs 100) or ribociclib (149 vs 102) compared with palbociclib (3,182 vs 4,118), consistent with their later approvals.[8,9] Consequently, there is uncertainty about the HCRU and costs associated with abemaciclib and ribociclib in both studies. In our study, mean treatment duration was approximately 20 months, in line with PFS from recent US real-world studies.[49–51] Therefore, considering the long-term use of branded CDK4/6is, choice of treatment could have a significant financial impact for payers, should total cost difference be close to our estimates (eg, an incremental PPPM cost of $4,268 for abemaciclib vs palbociclib), and significant. Approximately 164,000 women are living with mBC in the US,[3] and their overall healthcare costs are high[4] and expected to increase.[5] Additional studies that include more patients taking abemaciclib and ribociclib are needed to better understand if there are cost differences between the CDK4/6is and to assess association with tolerability. Furthermore, patients with use of multiple CDK4/6is in this study were excluded, a patient group that may be of interest for future research.

Our findings may not be generalizable to the uninsured population or populations insured through other health plans; however, to address variability across health plans and provider contracts, Optum performs standardization of prices to increase database generalizability, and the prices used for the analysis reflect allowed payments. Similarly, two-thirds of our study population received their treatment via Medicare Advantage. Although enrollment in private Medicare Advantage plans increased from 28% in 2013 to 46% in 2022, and a Commonwealth Fund policy brief suggests that beneficiaries enrolled in Medicare and Medicare Advantage plans are similar after removing patients on special needs plans, our Medicare Advantage subgroup data may not be generalizable to patients receiving Medicare or

who have a different Medicare plan type.[52,53] Furthermore, rural populations are much less represented in the Optum database than urban populations. Due to unavailability of patient and provider ZIP Codes, the study was not able to adjust for patients' geographic location (ie, rural/urban) or account for distance between patients and healthcare facilities.

Conclusions

This study compared HCRU and associated costs between palbociclib, abemaciclib, and ribociclib for treating patients with HR+/HER2– mBC in the first- and second-line settings. All-cause HCRU and costs were generally similar between the CDK4/6is, although compared with palbociclib, there were more IP admissions, higher outpatient medical costs, and a trend for higher total medical costs, driven primarily by higher IP costs with abemaciclib. In addition, there was a strong trend for higher medical costs during the initial treatment period with abemaciclib. There were no differences in costs between palbociclib and ribociclib. Further research with larger abemaciclib and ribociclib cohorts, overall and in important subgroups such as patients 65 years and older, and deeper exploration of types and underlying causes of costs is warranted to reduce uncertainty about the costs of abemaciclib and ribociclib and to refine the understanding of CDK4/6i-related costs in all phases of treatment, including those related to variations in the AE/tolerability profiles between the CDK4/6is. This may help reduce medical and IP costs, considering CDK4/6is are oral treatments, to support a cost-minimization strategy for mBC, which carries a high financial burden.

Abbreviations

AE, adverse event; BC, breast cancer; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CDM, Clinformatics DataMart; CNS, central nervous system; ECG, electrocardiogram; ED, emergency department; HCRU, healthcare resource utilization; HR+/HER2– hormone receptor-positive/human epidermal growth factor receptor 2-negative; IP, inpatient; IRR, incidence rate ratio; mBC, metastatic breast cancer; NCICI, National Cancer Institute's Comorbidity Index; PFS, progression-free survival; PPPM, per patient per month; QoL, quality of life; SD, standard deviation; sIPTW, stabilized inverse probability treatment weighting; SMD, standardized mean difference; US, United States.

Data Sharing Statement

All data generated or analyzed during this study are included in this published article and its supplementary information files.

Ethics Approval

This was a retrospective database study without prospectively enrolled participants. All database records are de-identified and fully compliant with US patient confidentiality requirements, including the Health Insurance Portability and Accountability Act of 1996. The data used for this study did not involve the interaction or interview with any subjects and the data does not include any individually identifiable data and, as such, is not research involving human subjects. Accordingly, ethical approval was not required for this study.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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