Comparison of healthcare resource utilization and costs of patients with HR+/HER2- advanced breast cancer treated with ribociclib versus other CDK4/6 inhibitors

Rebecca Burnea, Sanjeev Balub, Annie Guérina, Rebecca Bungayc, Roxana Sine and Mary Lisha Paulb

aAnalysis Group, Montréal, Canada; bHealth Economics and Outcomes Research, Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA

ABSTRACT

Aims: To assess healthcare resource utilization (HRU) and healthcare costs among women with hormone receptor-positive and human epidermal growth factor receptor 2-negative advanced breast cancer (HR+/HER2- aBC) treated with cyclin-dependent kinases 4 and 6 (CDK4/6) inhibitors.

Methods: Women with HR+/HER2- aBC, initiating CDK4/6 inhibitor treatment were identified using IBM MarketScan Commercial and Medicare Supplemental databases (Q1/2000–Q3/2018). Based on the first CDK4/6 inhibitor patients received (index therapy), three cohorts were identified: abemaciclib, palbociclib, and ribociclib. The baseline period (six months preceding treatment initiation) was used to describe patient characteristics. All-cause HRU and direct total healthcare costs (medical and pharmacy) from treatment initiation until the earliest of the end of index therapy, continuous health plan enrollment, or data availability, were compared for the ribociclib cohort versus the abemaciclib and palbociclib cohorts, separately, using weighted regression analyses balanced on baseline covariates.

Results: Average age at treatment initiation was ~60 years and the majority of patients were postmenopausal (abemaciclib: 92%; palbociclib: 92%; ribociclib: 79%). Average follow-up duration was 3.9, 8.8, and 5.9 months for the abemaciclib, palbociclib, and ribociclib cohorts, respectively. After reweighting, HRU was not statistically different between the ribociclib and abemaciclib cohorts, however, the ribociclib cohort incurred significantly lower total healthcare costs (~$5,452; 95% CI: ~$8,726; ~$1,139, p = .01). Medical costs (driven by outpatient costs) and pharmacy costs (driven by CDK4/6 inhibitor costs) were significantly lower for the ribociclib cohort. Among the reweighted ribociclib and palbociclib cohorts, HRU and total healthcare costs were not statistically different, although the ribociclib cohort had lower outpatient costs per-patient-per-month (~$1,245, 95% CI: ~$2,349; ~$37, p = .04).

Limitations: Due to the retrospective, observational design, treatment cohorts were not randomly assigned.

Conclusions: During CDK4/6 inhibitor therapy, ribociclib patients tended to incur lower medical and pharmacy costs than abemaciclib patients. Among ribociclib and palbociclib patients, HRU and healthcare costs were similar.

Introduction

It was recently estimated that over 150,000 women in the United States (US) have metastatic breast cancer (mBC)1. Treatments can minimize disease progression and improve quality of life in patients with mBC2–4, though most require multiple lines of therapy to achieve clinical benefit5,6. Previously, endocrine therapy (ET) and chemotherapy alone or in combination were common treatments for mBC5. However, agents that inhibit cyclin-dependent kinases 4 and 6 (CDK4/6) have recently become the standard of care for women with advanced BC (aBC) or mBC that is hormone receptor-positive and human epidermal growth factor receptor 2-negative (HR+/HER2-), the most common subtype of BC6–9.

The first CDK4/6 inhibitor, palbociclib, was approved by the Food and Drug Administration (FDA) in February 201510, followed by ribociclib in March 2017 (currently the only treatment specifically indicated for use in premenopausal women)11, and abemaciclib in September 201712. To date, several clinical studies have confirmed the benefit of CDK4/6 inhibitors as first-line therapy for HR+/HER2- aBC13–15, which has been noted regardless of menopausal status, prior therapies, and metastatic sites16. For example, results from three phase III studies, MONALEESA-2, MONALEESA-3, and MONALEESA-7, reported significantly longer progression-free
survival (PFS) in postmenopausal women with HR+/HER2- aBC treated with ribociclib + ET versus placebo + ET, and both MONALEESA-3 and MONALEESA-7 reported significantly longer overall survival (OS)\textsuperscript{13,17–20}. Similarly, the PALOMA-3 phase III clinical study of palbociclib + ET, as well as the MONARCH 2 and MONARCH 3 phase III studies of abemaciclib + ET, also reported significantly better outcomes compared to placebo + ET, regardless of menopausal status\textsuperscript{14,15,21–23}.

Despite the clear clinical benefit of CDK4/6 inhibitors for the treatment of HR+/HER2- aBC, evidence is needed regarding their comparative healthcare resource utilization (HRU) and economic outcomes. Although several cost-effectiveness models in different countries have previously been published\textsuperscript{24–27}, it is important to understand the real-world impact of these treatments from the payer perspective, particularly as all three CDK4/6 inhibitors may differ in terms of efficacy and tolerability which may impact HRU and healthcare costs. To help fill this knowledge gap, this study compares the HRU and healthcare costs of pre- and postmenopausal women diagnosed with HR+/HER2- aBC treated with ribociclib versus abemaciclib and ribociclib versus palbociclib in real-world practice from a US commercial payer perspective.

**Methods**

**Data source**

To conduct this analysis, data from the IBM MarketScan Commercial and Medicare Supplemental databases from Q1/2000 until Q3/2018 were used, which includes the medical claims of insured employees and their dependents, as well as Medicare-eligible retirees with employer-provided Medicare Supplemental plans. The database consists of medical and pharmacy claims of over 160 employers, including more than 40 health plans (payers), representing more than 39 million covered lives in the most recent full data year. All census regions are well represented, although there is a slightly higher representation from the South and North Central (Midwest) regions. The database includes detailed information on history of health plan enrollment, demographics, medical care received across different settings, diagnoses, procedures, as well as medications. The data are de-identified and comply with the confidentiality requirements of the Health Insurance Portability and Accountability Act.

**Study design**

An observational retrospective cohort design using US administrative insurance claims data was used. The index date was defined by the first observed claim for a CDK4/6 inhibitor (i.e. index therapy) among adult women with HR+/HER2- aBC. The baseline period included the 6-months preceding the index date and the follow-up period spanned from the index date to the earliest of the end of continuous health plan enrollment or data availability. Study outcomes were measured during the study period, which began on the index date and terminated at the end of the index therapy, patients’ continuous health plan enrollment, or data availability, whichever occurred first.

**Sample selection**

Adult women with HR+/HER2- aBC and evidence of treatment with a CDK4/6 inhibitor regardless of reproductive status and the line of therapy were included in this study. They were required to have \( \geq 6 \) months of continuous health plan coverage prior to, and \( \geq 1 \) month of continuous health plan coverage after, the index date, and \( \geq 2 \) claims with a diagnosis for BC (International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM] code: 174.xx and International Classification of Diseases, 10th Revision, Clinical Modification code [ICD-10-CM] code: C50.xx [excluding C50.x2 – male BC]) separated by at least 30 days. Additionally, they were required to have aBC identified based on the presence of \( \geq 2 \) medical claims for a secondary neoplasm (ICD-9-CM codes: 196.xx–197.xx, 198.xx, ICD-10-CM codes: C77.xx, C78.xx, C79.xx) which has been previously established and used in several studies to evaluate various cancer-related outcomes\textsuperscript{28–32}. Based on the index CDK4/6 inhibitor treatment received, three mutually-exclusive cohorts of patients were identified: \textit{abemaciclib cohort, palbociclib cohort, and ribociclib cohort}.

**Study outcomes**

Patient characteristics were summarized descriptively on the index date (demographics, calendar year of the initiation of the studied line of therapy, reproductive status [identified by a previously published claims-based algorithm]\textsuperscript{28}, and prior treatment for aBC) and during the baseline period (time from aBC diagnosis to index date, number of prior lines of therapy for aBC, prior use of chemotherapy and radiation therapy, organ-level metastatic sites, and Quan-Charlson Comorbidity Index [CCI] score\textsuperscript{33}).

HRU and healthcare costs were measured during the study period. Since this period differed in duration between patients, HRU was reported as the number of visits or services per-patient-per-6-months (PPP6M), and healthcare costs were reported per-patient-per-month (PPPMM); the different denominators (one month/six months) were chosen based on the relative magnitudes of the rates, but have no consequence on the final interpretations. All-cause HRU...
components (including number of inpatient [IP] admissions, IP days, days with emergency room [ER] services, and days with outpatient [OP] services) were reported. Direct total healthcare cost components included total medical costs which were further divided into IP, ER, and OP cost components, as well as total pharmacy costs and those related specifically to CDK4/6 inhibitors. Healthcare costs were measured from a payers’ perspective and reflected the total amount reimbursed by the private payer and the amount covered by the coordination of benefits, excluding patients’ payment (i.e. deductibles and copayments). Costs were adjusted for inflation using the US Medical Care Consumer Price Index from the Bureau of Labor Statistics from the US Department of Labor, and were reported in 2018 US dollars (the latest year observed in the data analyzed).

Statistical analysis

Entropy balancing was used to balance baseline characteristics that may have an impact on the differences in outcomes between cohorts. This technique adjusts for inequalities between treatment groups by calculating and applying weights using an algorithm that attempts to choose weights that deviate as little as possible from unit weights, while making the distribution of the matched variables have the exact same moments (e.g. mean, standard deviation [SD]). Thus, the distribution of predefined patient characteristics in the reweighted populations, such as age or reproductive status, will be identical between treatment cohorts. Entropy balance was chosen over other commonly used weighting methods, such as inverse probability of treatment weighting, because it achieves better covariate balance without relying on correct propensity score model specification, and has thus become increasingly used in observational studies. As such, the abemaciclib and palbociclib cohorts were separately reweighted so that the overall distribution of a priori selected relevant patient characteristics (i.e. age, line of therapy, reproductive status, CCI score, and metastatic sites (number of metastatic sites, metastasis of the lymph nodes only, and visceral metastases)) had the exact same means and SDs as the distribution of these characteristics in the ribociclib cohort.

HRU PPP6M was defined as the total number of visits or services for a patient that occurred during the study period divided by the duration of the study period (in months), and were descriptively summarized. Statistical comparisons for all healthcare cost components were conducted for the ribociclib cohort versus the abemaciclib cohort and the ribociclib cohort versus the palbociclib cohort, separately. The differences in costs between treatment cohorts were estimated using weighted two-part models, where the first part was a logistic model with a binomial distribution (used to predict the likelihood of having a cost greater than zero), and the second part was a GLM with a log link and a gamma distribution (to estimate average costs for patients with non-zero costs). Results were reported as cost differences with 95% CIs and p-values.

As a sensitivity analysis, the comparisons for all HRU and healthcare cost components were replicated using regression analyses without reweighting by entropy balancing, adjusting for the baseline covariates included in the main analyses (i.e. age, line of therapy, reproductive status, CCI score, and metastatic sites).

Results

A total of 4,320 HR+/HER2- women received treatment with CDK4/6 inhibitor for aBc and were included in the analyses. Among them, 100 received abemaciclib, 4,118 received palbociclib, and 102 received ribociclib (Figure 1).

Patient characteristics

Prior to reweighting, the majority of patients across all treatment cohorts had postmenopausal reproductive status, with the proportion appearing to differ across cohorts (92% in the abemaciclib and palbociclib cohorts versus 79% in the ribociclib cohort; Table 1). More than half of the women in each cohort received the index CDK4/6 inhibitor in the first- or second-line of therapy (first line; abemaciclib: 30%; palbociclib: 31%; ribociclib: 40%; second line; abemaciclib: 22%; palbociclib: 24%; ribociclib: 23%). At index therapy initiation, multiple metastatic sites other than lymph nodes were observed more frequently in the abemaciclib cohort (51%) than the palbociclib (40%) and ribociclib (38%) cohorts. The average duration of the study period (i.e. the observed duration of index therapy) was 3.9 months for the abemaciclib cohort, 8.8 months for the palbociclib cohort, and 5.9 months for the ribociclib cohort. At the end of this period, the proportions of patients who remained on treatment were 81%, 57%, and 66% in the abemaciclib, palbociclib, and ribociclib cohorts, respectively.

After reweighting, the study cohorts were well-balanced on relevant patient characteristics, such that, for example, postmenopausal status was observed in 79% of patients across all treatment cohorts (Table 1). The proportion of patients who received the index CDK4/6 inhibitor in first-line of therapy was 39% in the abemaciclib cohort and 40% in both the palbociclib and ribociclib cohorts; the proportion who received the index CDK4/6 inhibitor in second-line of therapy was 26% in the abemaciclib cohort and 23% in the palbociclib and ribociclib cohorts. The year of initiation of the first CDK4/6 inhibitor therapy still differed slightly across treatment cohorts due to the variation in drug approval.
dates; as such, the majority of women in the abemaciclib cohort initiated treatment in 2018 (79%), palbociclib in 2015–2016 (59%), and ribociclib in 2017 (65%). The average age at index therapy initiation was 59 years across all treatment cohorts, and the most common metastatic sites observed were the bone and bone marrow (abemaciclib: 72%; palbociclib: 75%; ribociclib: 70%). The median CCI score was 6.0 in all treatment cohorts.

**HRU**

During the study period and before reweighting, patients had an average of 0.7 IP admissions PPP6M in the abemaciclib cohort, 0.4 admissions PPP6M in the palbociclib cohort, and 0.5 admissions PPP6M in the ribociclib cohort. The abemaciclib cohort appeared to have a higher average number of IP days (4.6 days PPP6M) compared to the palbociclib (2.4 days PPP6M) and ribociclib (2.1 days PPP6M) cohorts. The abemaciclib, palbociclib, and ribociclib cohorts had an average number of days with ER services of 0.9, 0.6, and 1.1 PPP6M, respectively, and an average number of days with OP services of 26.9, 23.7, and 24.4 PPP6M, respectively (Figure 2).

Although HRU outcomes were not significantly different between the reweighted ribociclib and abemaciclib cohorts during the study period, all categories showed a numerical trend towards a lower rate of events in the ribociclib cohort compared to the abemaciclib cohort, including the number of IP admissions (IRR: 0.57, \( p = .21 \)), IP days (IRR: 0.43, \( p = .10 \)), days with ER services (IRR: 0.90, \( p = .77 \)), and days with OP services (IRR: 0.88, \( p = .13 \); Figure 2).

Comparisons between the reweighted ribociclib and palbociclib cohorts during the study period yielded no observable differences for the number of IP admissions (IRR: 1.13, \( p = .71 \)), IP days (IRR: 0.86, \( p = .69 \)), days with ER services (IRR: 1.56, \( p = .14 \)), or days with OP services (IRR: 1.01, \( p = .91 \); Figure 2).

Results from the sensitivity analysis using standard regression models without entropy balancing were comparable to the main findings of the study, with the exception of a significant difference observed in the number of IP days, which were fewer in the ribociclib cohort compared to the abemaciclib cohort (adjusted IRR: 0.25, \( p = .01 \); Supplementary Materials Figure S1).

**Healthcare costs**

During the study period and before reweighting, total healthcare costs tended to be higher on average among the
### Table 1. Description of baseline characteristics.

| Demographics (as of the index date) | Before reweighting | After reweighting |
|-------------------------------------|--------------------|-------------------|
| **Age at the initiation of first CDK4/6 inhibitor therapy (years)** | 59.5 ± 11.7 [59.0] | 59.4 ± 11.3 [59.0] | 59.3 ± 11.4 [59.0] |
| **Region, N (%)** | | | |
| North Central | 19 (19.0%) | 92 (23.8%) | 26 (25.5%) | 23 (23.1%) | 953 (23.1%) | 26 (25.5%) |
| Northeast | 27 (27.0%) | 863 (21.0%) | 11 (10.8%) | 22 (21.9%) | 886 (21.5%) | 11 (10.8%) |
| South | 42 (42.0%) | 1,683 (40.9%) | 43 (42.2%) | 42 (42.1%) | 1,684 (40.9%) | 43 (42.2%) |
| West | 12 (12.0%) | 590 (14.3%) | 22 (21.6%) | 13 (12.9%) | 595 (14.4%) | 22 (21.6%) |
| **Type of health plan, N (%)** | | | |
| CDHP and HDHP | 17 (17.0%) | 478 (11.6%) | 13 (12.7%) | 18 (18.4%) | 515 (12.5%) | 13 (12.7%) |
| Comprehensive | 10 (10.0%) | 490 (11.9%) | 13 (12.7%) | 9 (9.3%) | 438 (10.6%) | 13 (12.7%) |
| HMO and POS with capitation | 10 (10.0%) | 531 (12.9%) | 12 (11.8%) | 8 (7.9%) | 541 (13.1%) | 12 (11.8%) |
| POS without capitation and EPO | 12 (12.0%) | 286 (6.9%) | 9 (8.8%) | 13 (12.9%) | 285 (6.9%) | 9 (8.8%) |
| PPO | 49 (49.0%) | 2,297 (55.8%) | 55 (53.9%) | 51 (51.3%) | 2,305 (56.0%) | 55 (53.9%) |
| Unknown | 2 (2.0%) | 36 (0.9%) | 0 (0.0%) | 2 (2.3%) | 33 (0.8%) | 0 (0.0%) |
| **Year of the initiation of first CDK4/6 inhibitor therapy, N (%)** | | | |
| 2015 | 0 (0.0%) | 1,087 (26.4%) | 0 (0.0%) | 0 (0.0%) | 1,023 (24.8%) | 0 (0.0%) |
| 2016 | 0 (0.0%) | 1,424 (34.6%) | 0 (0.0%) | 0 (0.0%) | 1,416 (34.4%) | 0 (0.0%) |
| 2017 | 26 (26.0%) | 1,116 (27.1%) | 66 (64.7%) | 21 (21.2%) | 1,141 (27.7%) | 66 (64.7%) |
| 2018 | 74 (74.0%) | 491 (12.1%) | 12 (11.8%) | 8 (7.9%) | 573 (13.0%) | 12 (11.8%) |
| **Reproductive status** | | | |
| Postmenopausalb | 92 (92.0%) | 3,788 (92.0%) | 81 (79.4%) | 79 (79.4%) | 3,264 (79.3%) | 81 (79.4%) |
| **Prior treatment for aBC** | | | |
| Time from aBC diagnosis to index date (months)b, mean ± SD [median] | 34.2 ± 39.9 [17.6] | 26.3 ± 32.3 [14.7] | 20.7 ± 26.9 [6.8] | 20.7 ± 26.9 [8.5] | 20.7 ± 27.0 [8.1] | 20.7 ± 26.9 [6.8] |
| Number of prior lines of therapy for aBC, N (%) | | | |
| No prior lines of therapy | 30 (30.0%) | 1,291 (31.4%) | 41 (40.2%) | 38 (38.5%) | 1,654 (40.2%) | 41 (40.2%) |
| 1 | 22 (22.0%) | 999 (24.3%) | 23 (22.5%) | 26 (26.2%) | 930 (22.6%) | 23 (22.5%) |
| 2 | 15 (15.0%) | 617 (15.0%) | 14 (13.7%) | 11 (11.5%) | 564 (13.7%) | 14 (13.7%) |
| 3+ | 33 (33.0%) | 1,211 (29.4%) | 24 (23.5%) | 24 (23.8%) | 971 (23.5%) | 24 (23.6%) |
| Received prior chemotherapy, N (%) | | | |
| Received prior radiation therapy, N (%) | | | |
| Organ-level metastatic sites,c, N (%) | | | |
| Multiple metastatic sites (excluding lymph nodes) | | | |
| Number of metastatic sites (excluding lymph nodes)d, mean ± SD [median] | 1.8 ± 1.2 [2.0] | 1.5 ± 1.0 [1.0] | 1.5 ± 0.9 [1.0] | 1.5 ± 0.9 [1.0] | 1.5 ± 0.9 [1.0] | 1.5 ± 0.9 [1.0] |
| Bone and bone marrow | 75 (75.0%) | 3,031 (73.6%) | 71 (69.6%) | 72 (70.0%) | 3,078 (74.8%) | 71 (69.6%) |
| Visceralb | 52 (52.0%) | 1,653 (40.1%) | 40 (39.2%) | 39 (39.2%) | 1,614 (39.2%) | 40 (39.2%) |
| Lymph nodes | 29 (29.0%) | 1,243 (30.2%) | 22 (21.6%) | 25 (24.6%) | 1,301 (31.6%) | 22 (21.6%) |
| Lymph nodes only | 1 (1.0%) | 184 (4.5%) | 3 (2.9%) | 1 (0.6%) | 154 (3.7%) | 3 (2.9%) |
| Central nervous system | 16 (16.0%) | 354 (8.6%) | 15 (14.7%) | 11 (10.7%) | 352 (8.6%) | 15 (14.7%) |
| Disseminated neoplasm | 0 (0.0%) | 108 (2.6%) | 6 (5.9%) | 0 (0.0%) | 100 (2.4%) | 6 (5.9%) |
| Baseline CCId, mean ± SD [median] | 6.8 ± 1.0 [6.0] | 6.8 ± 1.1 [6.0] | 6.7 ± 1.1 [6.0] | 6.7 ± 1.1 [6.0] | 6.8 ± 1.1 [6.0] | 6.7 ± 1.1 [6.0] |

**Abbreviations.** aBC, Advanced breast cancer; CCI, Charlson Comorbidity Index; CDHP, Consumer-driven health plan; EPO, Exclusive provider organization; HDHP, High-deductible health plan; HMO, Home health organization; CDK4/6, Cyclin-dependent kinase 4 or 6; ICD-9-CM, International Classification of Diseases, 9th Revision, Clinical Modification; ICD-10-CM, International Classification of Diseases, 10th Revision, Clinical Modification; POS, Point of service; PPO, Preferred provider organization; SD, Standard deviation.

*aThe baseline period was defined as the 6 months preceding the index date (i.e. date of initiation of first CDK4/6 inhibitor therapy).*

*bPatient characteristics were weighted using entropy balancing on age, line of therapy, reproductive status, CCI, time between diagnosis and treatment with a CDK4/6 inhibitor, visceral metastatic sites, and the number of metastatic sites.*

*cOrgan-level metastatic sites were assessed by ICD-9-CM and ICD-10-CM diagnosis codes any time prior to the line of therapy initiation up until 30 days after the line of therapy initiation.*

*dSource: Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10-CM administrative data. Med Care. 2005; 43(11): 1130–1139.*
abemaciclib cohort ($25,920 PPPM) than the palbociclib ($19,977 PPPM) and ribociclib ($19,176 PPPM) cohorts. This difference seemed to be driven largely by the total medical costs, which appeared to be greater in the abemaciclib ($12,378 PPPM) than the palbociclib ($7,928 PPPM) and ribociclib ($7,136 PPPM) cohorts. By further examining the medical cost components, a similar pattern was observed for IP costs (abemaciclib: $3,748 PPPM; palbociclib: $1,926 PPPM; ribociclib: $1,871 PPPM) and OP costs (abemaciclib: $8,298 PPPM; palbociclib: $5,727 PPPM; ribociclib: $4,578 PPPM), with OP costs being the primary driver of the total medical costs in all three patient cohorts. On the contrary, ER costs appeared to be largely similar between treatment cohorts (abemaciclib: $318 PPPM; palbociclib: $260 PPPM; ribociclib: $683 PPPM). The observed total pharmacy costs were also greater in the abemaciclib cohort ($13,542 PPPM) than the palbociclib ($12,049 PPPM) and ribociclib ($12,040 PPPM) cohorts, with CDK4/6 inhibitor costs being the primary contributor to total pharmacy costs in all three patient cohorts (abemaciclib: $13,218 PPPM; palbociclib: $11,646 PPPM; ribociclib: $11,763 PPPM; Figure 3).

Total healthcare costs were significantly lower in the reweighted ribociclib cohort compared to the abemaciclib cohort during the study period (cost difference: $5,452, p = .01). Specifically, the ribociclib cohort had significantly lower medical costs (cost difference: $3,916, p = .05) and total pharmacy costs (cost difference: $1,536, p = .01). With regards to individual medical cost components, the ribociclib cohort showed significantly lower OP costs compared to the abemaciclib cohort (cost difference: $4,134, p < .01); however, IP costs (cost difference: $5,452, p = .01) and ER costs (cost difference: $450, p = .14) did not differ significantly between the two reweighted patient cohorts. The difference in total pharmacy costs between cohorts was driven by the

Figure 2. Comparison of healthcare resource utilization during index therapy1. Abbreviations. HRU, Healthcare resource utilization; PPP6M, Per-patient-per-6-months; SD, Standard deviation. Notes. [1] Healthcare resource utilization was measured between the index date and the observed end of index therapy. [2] The adjusted incidence rate ratio and confidence intervals for each outcome were estimated using a negative binomial regression, adjusted for age, line of therapy, reproductive status, Charlson Comorbidity Index, and metastatic sites.

Figure 3. Description of healthcare costs during index therapy1,2,3. Abbreviations. PPPM, Per-patient-per-month; USD, United States dollars. Notes. [1] Healthcare costs were measured between the index date and the observed end of index therapy. [2] Healthcare costs were measured from a payer’s perspective (i.e. health plan payment + coordination of benefits, excluding patients’ payment), adjusted for inflation using the United States Medical Care Consumer Price Index, and reported in 2018 USD. [3] PPPM healthcare costs were defined as the total costs reported on a monthly basis to account for different durations of line of therapy.
lower costs of CDK4/6 inhibitors for the ribociclib cohort compared to the abemaciclib cohort (cost difference: $-1,417, p = .01; Figure 4).

There were no significant differences in total healthcare costs between the reweighted ribociclib and palbociclib cohorts during the study period (cost difference: $-859, p = .56). Specifically, there were no differences in medical costs (cost difference: $-841, p = .54) or total pharmacy costs (cost difference: $-18, p = .92). No significant differences were observed between cohorts with respect to IP costs (cost difference: $-6, p = .94) or ER costs (cost difference: $419, p = .18), although there were significantly lower OP costs observed in the ribociclib cohort compared to the palbociclib cohort (cost difference: $-1,245, p = .04; Figure 4).

Results from the sensitivity analysis using standard regression models without entropy balancing were comparable to the main findings of the study, with the exception of a significant difference observed in IP costs, which were lower in the ribociclib cohort compared to the abemaciclib cohort (adjusted cost difference: $-3,398, p = .01; Supplementary Materials Figure S2).

**Discussion**

To our knowledge, this is the first study offering a comparative assessment of real-world economic outcomes of adult women with HR+/HER2- aBC receiving the CDK4/6 inhibitors abemaciclib, palbociclib, or ribociclib. Analyses show that the total healthcare costs for women with aBC receiving CDK4/6 inhibitor treatment tended to be higher in the abemaciclib cohort compared to the ribociclib cohort, while the palbociclib and the ribociclib cohorts had similar total healthcare costs overall.

Among all women with HR+/HER2- aBC receiving a CDK4/6 inhibitor who were included in this study, the vast majority were postmenopausal, with a lower prevalence among those treated with ribociclib compared to abemaciclib or palbociclib. One reason for this difference might stem from the fact that, unlike abemaciclib and palbociclib, ribociclib is currently the only treatment option specifically indicated for use in premenopausal women following results of the randomized phase III trial (MONALEESA-7) which demonstrated improved PFS and OS with ribociclib treatment specifically in premenopausal women with HR+/HER2- aBC.

The time from the first aBC diagnosis to treatment initiation also appeared to be shorter in the ribociclib cohort compared to the abemaciclib or palbociclib cohorts. These variations between cohorts, along with other observed baseline differences such as metastatic sites, were balanced between cohorts using entropy balancing for the purpose of the HRU and cost analyses.

Comparatively, women treated with ribociclib or palbociclib tended to have a similar number of HRU events which translated to similar incurred costs, with the exception of OP costs which were $1,245 lower PPPM in the ribociclib cohort than in the palbociclib cohort. Pharmacy costs while on CDK4/6 inhibitor-based therapy were also similar between the two treatment cohorts. Despite the similar rate of HRU events between patients treated with ribociclib compared to abemaciclib, the ribociclib cohort incurred $3,916 less in medical costs PPPM than the abemaciclib cohort, with differences largely driven by lower OP ($4,134 PPPM) costs. Compared to women in the abemaciclib cohort, those in the ribociclib cohort also incurred $1,536 less in pharmacy costs PPPM driven by lower CDK4/6 inhibitor costs ($1,417 PPPM), which accounted for the largest component of pharmacy costs among this sample. Some recent studies have applied cost-effectiveness models to evaluate the CDK4/6 inhibitors, although differences in the measured outcomes and reported currencies limit comparisons between studies.

For example, Giuliani & Bonetti assessed the pharmacological costs of the three agents expressed in 2020 euros based on drug costs from a pharmacy in Italy and found that ribociclib was less expensive than abemaciclib and palbociclib. The current study provides a novel comparison of the real-world economic burden for women with HR+/HER2- aBC receiving CDK4/6 inhibitors from a US payer’s perspective, particularly as the three CDK4/6 inhibitors may differ in terms of efficacy and tolerability, which could have an impact on HRU and costs in this population.

While several trials have demonstrated the clinical benefit of CDK4/6 inhibitors for women with HR+/HER2- aBC, the availability of comparative data between agents is largely lacking. An indirect meta-analysis compared the effectiveness of abemaciclib, palbociclib, and ribociclib (plus ET) in women...
with HR+/HER2- mBC (specifically, estrogen receptor positive [ER+]) and found no differences in either first- or second-line therapy based on measures of PFS or overall response rate, albeit with some differences in toxicity profiles which may dictate the choice of treatment for certain patients. It should be noted that at the time of completion of this meta-analysis, OS data were not available for the CDK4/6 inhibitors. Given that recent evidence has highlighted differences in OS between the CDK4/6 inhibitors, real-world analyses of OS are warranted. Current estimates of the economic burden of aBC are also lacking in literature, particularly since the introduction of newer CDK4/6 inhibitors for women with HR+/HER2- aBC. Comparative assessments of HRU and costs between agents are necessary to evaluate CDK4/6 inhibitors from a payer’s perspective as this study reveals the high monthly costs associated with CDK4/6 inhibitor treatment in this population. Prior to the approval of CDK4/6 inhibitors, some studies evaluated the cost of care in aBC/mBC patients. However, the opportunity for comparison between our findings and those of prior studies is limited as none to date have reported HRU and costs associated with CDK4/6 inhibitor treatment in women with HR+/HER2- aBC. Nevertheless, it is evident that treatment-related costs (i.e., drug administration, toxicity management, medical follow-up) account for a large portion of the overall incurred costs in women with mBC, with OP visits in particular driving total medical costs. These observations are consistent with findings of the current study.

The findings of this study are important, as a meaningful reduction in HRU and consequent reduction in costs align with the goals of programs such as the Oncology Care Model, the Centers for Medicare & Medicaid Services Stars Program, and the Quality Oncology Practice Initiative (QOPI) Certification Program, which provide incentives to caregivers and practices for improved quality of care.

**Limitations**

The findings of this study should be interpreted in light of certain limitations. First, given that there is no information in claims data to directly identify women with aBC and HR+/HER2- status, an algorithm based on treatments and procedures, recommendations from the National Comprehensive Cancer Network guidelines, and FDA drug approvals were used to identify study participants. Second, as this was a retrospective observational study, women with HR+/HER2- aBC were not randomly assigned to the different treatment cohorts. Additionally, the sample size and follow-up duration was limited for the abemaciclib and ribociclib cohorts. Third, patients had varying lengths of follow-up and menopausal status, and were included in the study population regardless of which line of therapy they received their first CDK4/6 inhibitor in. To mitigate these limitations, study outcomes were reported on a monthly-basis to account for the variability in the study period, and menopausal status and lines of therapy were among the covariates used to reweight the study cohorts using entropy balancing. It should be noted that the average length of follow-up in this study is not indicative of treatment duration or effectiveness, as a large proportion of patients were still on their index therapy at the end of data availability. It should also be noted that since the study was conducted shortly after the approval of abemaciclib, management of new symptoms for this agent may have contributed to the associated HRU and costs.

Fourth, the study sample is limited to commercially insured US employees and their dependents diagnosed with aBC, and thus the generalizability to the overall population of HR+/HER2- aBC women treated with CDK4/6 inhibitors, or those in other countries, may be limited. Additionally, the estimated costs were derived from the IBM MarketScan Research Databases and may differ by specific health plan.

Finally, this study was subject to common limitations inherent to claims databases, such as vulnerability to coding errors or data omission, and underreporting since diagnostic and procedure codes are recorded for reimbursement purposes.

**Conclusions**

This study compared HRU and healthcare costs of adult women with HR+/HER2- aBC receiving abemaciclib, palbociclib, or ribociclib using real-world data in the US. Results show that total healthcare costs PPPM while on treatment tended to be higher in the abemaciclib cohort compared to the ribociclib cohort, while the palbociclib and the ribociclib cohorts tended to have similar costs. As the present investigation was one of few early studies in the US demonstrating real-world evidence of treatment patterns, HRU, and costs among women with aBC treated with CDK4/6 inhibitors, more real-world comparative studies are warranted to determine long-term treatment patterns and outcomes in these patients.

**Transparency**

**Declaration of funding**

This study was sponsored by Novartis Pharmaceuticals Corporation. The study sponsor was involved in several aspects of the research including the study design, the interpretation of data, the writing of the manuscript, and the decision to submit the manuscript for publication.

**Declaration of financial/other interests**

SB, RS, and MLP are employees and stockholders of Novartis Pharmaceuticals Corporation.

RB, AG, and RB are employees of Analysis Group, Inc., a consulting company that has provided paid consulting services to Novartis Pharmaceuticals Corporation.

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**Author contributions**

All authors contributed significantly to the conception and design of the study.

RB and RB participated in the data analysis.

All authors participated in the interpretation of the data. All authors revised the manuscript critically for intellectual content and approved
the final version to be published. All authors, therefore, agree to be accountable for all aspects of the work.

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