

Effectiveness of ribociclib in metastatic breast cancer in one hospital in Bulgaria—results from real-world clinical practice

Mariyana Eneva^{1,2}, Petya Borisova³, Boryana Ivanova^{2,3}, Mila Petrova¹, Alexandra Savova^{2,3}, Manoela Manova^{2,3}

¹ Medical Oncology Clinic, MHAT Nadezhda, Sofia, Bulgaria

² Department “Organization and Economics of Pharmacy”, Faculty of Pharmacy, Medical University of Sofia, Sofia, Bulgaria

³ National Council on Prices and Reimbursement of Medicinal Products, Sofia, Bulgaria

Corresponding author: Manoela Manova (mmanova@pharmfac.mu-sofia.bg)

Received 5 March 2026 ♦ Accepted 18 March 2026 ♦ Published 7 April 2026

Citation: Eneva M, Borisova P, Ivanova B, Petrova M, Savova A, Manova M (2026) Effectiveness of ribociclib in metastatic breast cancer in one hospital in Bulgaria—results from real-world clinical practice. *Pharmacia* 73: 1-9. <https://doi.org/10.3897/pharmacia.73.e190655>

Abstract

Real-world evidence (RWE) complements randomized clinical trial data by demonstrating treatment effectiveness in routine practice and unselected populations. Despite the broad use of ribociclib, real-world data remain limited, particularly in Eastern Europe. This retrospective single-center analysis evaluated outcomes in Bulgarian patients treated with ribociclib and compared them with national and international evidence.

Of 156 patients, 71.8% received first-line therapy, and 80.2% had ECOG performance status 0. The clinical benefit rate was 86.9% overall and 90.9% in the first line. Median progression-free survival was 17.7 months overall and 19.9 months in the first line. Outcomes were comparable to pivotal phase III trials and national real-world data. In the Bulgarian setting, early use of ribociclib in patients with favorable performance status may achieve results similar to or better than those observed in broader national cohorts, highlighting the importance of optimal patient selection and management.

Keywords

Clinical benefit rate, endocrine therapy, overall survival, progression-free survival, ribociclib

Introduction

Breast cancer remains one of the leading causes of cancer-related mortality among women worldwide. The latest estimates from the European Commission Joint Research Centre indicate that breast cancer accounted for approximately 360,000 new cases across EU-27 countries in 2024, representing around 29% of all female cancers and a 1.7% decrease compared with the peak levels observed in 2022 (European Commission Joint Research Centre 2025a). In

Bulgaria, GLOBOCAN 2022 reported 3,565 new breast cancer cases, corresponding to 24.3% of all female cancers and an age-standardized incidence rate of 88 per 100,000 women—the lowest reported rate in the European Union (IARC 2022; European Commission Joint Research Centre 2025b). Peak incidence occurs among women aged 45–69 years, and roughly 67% of Bulgarian cases are diagnosed at stages I–II, although screening uptake remains suboptimal and uneven across regions (TBCT Bulgaria 2024). Taken together, these figures highlight the persistent and

substantial public health burden of breast cancer in Europe and, in particular, in Bulgaria, where approximately one in every 11 women faces a lifetime risk of developing the disease (European Commission 2020; European Commission Joint Research Centre 2025c).

For postmenopausal patients with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced or metastatic breast cancer (MBC), endocrine therapy remains the preferred initial treatment backbone (Cardoso et al. 2014). Over time, however, most patients develop resistance to endocrine therapy, forcing clinicians to seek strategies to prolong endocrine sensitivity or restore it after progression (Osborne and Schiff 2011).

Three cyclin-dependent kinase 4/6 (CDK4/6) inhibitors—palbociclib, ribociclib, and abemaciclib—are now approved for the management of HR+/HER2- advanced or metastatic breast cancer. They are used in combination with aromatase inhibitors (AIs) as first-line therapy in postmenopausal women and with fulvestrant in patients whose disease has progressed following prior endocrine therapy alone (European Society for Medical Oncology 2025). Three landmark phase III randomized controlled trials (RCTs)—MONALEESA-2, MONALEESA-3, and MONALEESA-7—have comprehensively evaluated ribociclib's efficacy and safety when combined with different endocrine partners in HR+/HER2- advanced breast cancer (Hortobagyi et al. 2016, 2018; Slamon et al. 2018, 2021a, 2021b; Tripathy et al. 2018). These trials enrolled a broad range of patients, including both pre- and postmenopausal women and men, with diverse treatment histories and disease presentations. Across the MONALEESA program, ribociclib plus endocrine therapy produced robust, clinically meaningful improvements in progression-free survival (PFS), for example, a median of 25.3 vs. 16.0 months in the MONALEESA-2 first-line setting, and long-term overall survival (OS), with a final MONALEESA-3 hazard ratio for OS of 0.72 (Hortobagyi et al. 2016, 2018; Slamon et al. 2018, 2021a, 2021b). Ribociclib, in particular, has shown consistent PFS benefits and an acceptable safety profile across premenopausal, perimenopausal, and postmenopausal subgroups (Hortobagyi et al. 2018; Tripathy et al. 2018). A recent meta-analysis of five major RCTs (total $n = 7,286$ patients) further confirmed that ribociclib plus endocrine therapy significantly improves both OS and PFS compared with endocrine therapy alone (Dhungana et al. 2025).

Real-world evidence (RWE) complements RCT data by describing how treatments perform in unselected patients managed under everyday clinical conditions. Despite the widespread adoption of ribociclib, published real-world data (RWD) remain relatively limited, and information from Eastern European countries is particularly sparse (Fountzilas et al. 2020; García-Trevijano Cabetas et al. 2021; Fernández-Cuerva et al. 2023; Queiroz et al. 2023; Provenzano et al. 2025; Cvetanović et al. 2026). In Bulgaria, ribociclib has been reimbursed since

2020 for HR+/HER2- locally advanced or metastatic breast cancer, either in combination with an AI or fulvestrant as initial endocrine-based therapy or after prior endocrine exposure, with its use accompanied by mandatory post-marketing effectiveness monitoring (Bulgarian National Health Insurance Fund 2020; National Council on Prices and Reimbursement 2023). To date, only one nationwide Bulgarian analysis has been published. Manova et al. evaluated outcomes in ribociclib-treated patients across the country and reported results broadly comparable to those of MONALEESA-2 and MONALEESA-3, thereby supporting the effectiveness of ribociclib in an unselected national cohort (National Council on Prices and Reimbursement 2023; Manova et al. 2023).

The aim of the present study was to evaluate real-world outcomes in patients with metastatic breast cancer treated with ribociclib at a single oncology hospital in Bulgaria and to compare these findings with available national real-world data from all Bulgarian hospitals.

Materials and methods

Data sources

The primary data source for this study is electronic health records (EHRs) collected from a single Bulgarian hospital. The retrospective analysis includes data ranging from 1 January 2018 to 31 December 2024. The data were extracted from both structured and unstructured free text using NLP algorithms. The analysis of these data was conducted using the Danny Platforms (Squiline Health, Sofia, Bulgaria; <https://squiline.com/products/danny-platform/>), an analytics platform that integrates large volumes of RWD from EHRs, leveraging embedded machine learning and NLP algorithms to extract information from free text in multiple languages.

Inclusion and exclusion criteria

In this real-world data study, we aligned patient selection as closely as possible with the MONALEESA-2, MONALEESA-3, and MONALEESA-7 trial populations to ensure comparability. MONALEESA-2 enrolled postmenopausal women with locally confirmed HR+, HER2-negative recurrent or metastatic breast cancer who had not received any prior systemic therapy for advanced disease. MONALEESA-3 included a broader population of postmenopausal women and men aged 18 years or older with HR+, HER2-negative advanced breast cancer; these patients were either treatment-naïve for advanced disease or had received up to one prior line of endocrine therapy but no prior chemotherapy for advanced disease. MONALEESA-7 focused on premenopausal or perimenopausal women aged 18 to 59 years with HR+, HER2-negative advanced breast cancer (Hortobagyi et al. 2016, 2018; Slamon et al. 2018, 2021a, 2021b; Tripathy et al. 2018).

Outcome measures

This real-world evidence study examined several key endpoints to comprehensively evaluate treatment outcomes. These included progression-free survival (PFS), defined as the probability of continuing treatment during the observation period without disease progression or being censored for reasons other than death from any cause; overall survival (OS), defined as the probability of continuing treatment during the observation period without censoring for death from any cause; and clinical benefit rate (CBR), calculated as the proportion of patients achieving complete response plus partial remission (CR + PR) plus stable disease (SD), assessed according to standard RECIST criteria.

Statistical considerations

For treatment outcome analyses, we estimated the survival functions for both OS and PFS using the Kaplan–Meier (product-limit) estimator, which is the standard approach for time-to-event data in oncology studies. The corresponding 95% confidence intervals for survival curves were calculated using Greenwood’s method to account for variability in the censoring pattern. For binomial variables such as response rates, we utilized the Wilson score method to derive 95% confidence intervals, which provide more stable estimates, particularly for outcomes with smaller event counts. Hazard ratios (HRs) were calculated using Cox proportional hazards regression models, specifically structured to align with the statistical methodology employed in the corresponding MONALEESA randomized controlled trials, thereby enabling direct and meaningful comparisons between trial and real-world populations.

In these analyses, we adjusted for key baseline covariates, including ECOG performance status, estrogen receptor (ER) status, progesterone receptor (PR) status, and patient age at treatment initiation. Other patient characteristics, such as whether patients had newly diagnosed metastatic disease, prior chemotherapy (CTx) exposure, or prior hormonal therapy, were not included as stratification factors in the primary analyses.

Results

Patient disposition

A total of 156 patients received ribociclib in combination with an aromatase inhibitor or fulvestrant for the treatment of HR+/HER2– advanced or metastatic breast cancer in routine clinical practice. Of these, 112 patients (71.8%) were treated with this regimen in the first-line setting, reflecting the growing preference for introducing CDK4/6 inhibition early in the course of metastatic disease.

Patient demographics and disease characteristics

Table 1 summarizes the baseline demographic and clinical characteristics of the study population. The median age at treatment initiation was 59 years (range 28–82), indicating that both younger and older adults were represented in this real-world cohort. This median age is broadly comparable to those reported in the pivotal MONALEESA-2 and MONALEESA-3 trials, where the median ages were 62 and 64 years, respectively (Hortobagyi et al. 2016; Slamon et al. 2018). Most patients had a good performance status: 96.2% had an ECOG score of 0 or 1, closely mirroring the eligibility criteria of the phase III trials and suggesting that the real-world population in this analysis was largely similar, in terms of functional status, to those enrolled in randomized controlled studies (Hortobagyi et al. 2016; Slamon et al. 2018).

Table 1. Patient characteristics.

Characteristics	Value	Ribociclib	
		N = 156	(%)
Age			
	Median (years)	59	
	Min–Max (years)	28–82	
ECOG N % (N = 156)			
	0	125	80.2
	1	25	16.0
	2	4	2.6
	3	1	0.6
	4	1	0.6
	5	-	-

Patient characteristic data from the entire Bulgarian population treated with ribociclib for metastatic breast cancer were used to place the outcomes of this single-center study into a broader national context. Table 2 compares ECOG performance status between the study cohort and the overall ribociclib-treated population. In the study cohort, 80.2% of patients had an ECOG score of 0, whereas in the national cohort, the largest subgroup comprised patients with ECOG 1 (53.7%), indicating that patients included in the single-center analysis had a better baseline

Table 2. ECOG status at a single medical center versus the overall patient population in Bulgaria.

Patient characteristic	Value	Ribociclib			
		Single center (n = 156)	Single center (%)	Overall cohort (n = 1484)	Overall cohort (%)
ECOG					
	0	125	80.2	511	34.5
	1	25	16.0	796	53.7
	2	4	2.6	107	7.2
	3	1	0.6	54	3.6
	4	1	0.6	14	0.9
	5	-	-	2	0.1

functional status and, consequently, a higher potential for more favorable clinical outcomes (National Council on Prices and Reimbursement 2023; Manova et al. 2023).

Clinical benefit rate

Comparison 1—all eligible patients (all treatment lines)

In the RWE, 20 patients (13.1%) had no response assessment. Among the patients with a response assessment, the CBR was 86.9%. Three patients had no data (Fig. 1).

Comparison 2—patients receiving 1 L treatment

In the RWE, 10 patients (9.1%) had no response assessment. Among the patients with a response assessment, the CBR was 90.9%. Two patients had no data (Fig. 2).

Progression-free survival

Comparison 1—all eligible patients (all treatment lines)

The median progression-free survival (PFS) in this real-world cohort was 17.7 months (95% CI: 15.8–23.4 months). The estimated probabilities of remaining progression-free at 6 and 12 months were 79% and 61%, respectively (Table 3, Fig. 3).

Comparison 2—patients receiving 1 L treatment

The median progression-free survival (PFS) in this real-world cohort was 19.9 months (95% CI: 17.1–24.5 months). The estimated probabilities of remaining progression-free at 6, 12, and 18 months were 81%, 62%, and 52%, respectively (Table 4, Fig. 4).

Overall survival

Comparison 1—all eligible patients (all treatment lines)

In the real-world evidence analysis, the median overall survival (OS) was 67.3 months (95% CI: 56.1–NR). The corresponding OS rates at subsequent time points are presented in Table 5 (Fig. 5).

Comparison 2—patients receiving 1 L treatment

In our real-world evidence analysis, the median overall survival (OS) was 67.3 months (95% CI: 56.1–not reached). The corresponding OS rates at successive time points are summarized in Table 6 (Fig. 6).

Discussion

The present analysis describes the outcomes of patients receiving ribociclib in combination with letrozole or fulvestrant in routine Bulgarian clinical practice. We examined clinical benefit rate, progression-free survival, and overall survival and compared these real-world outcomes with those from the MONALEESA-2, MONALEESA-3, and MONALEESA-7 trials, as well as with published real-world evidence from other countries (Hortobagyi et al. 2016, 2018; Slamon et al. 2018, 2021a, 2021b; Tripathy et al. 2018; Fountzilas et al. 2020; García-Trevijano Cabetas et al. 2021; Fernández-Cuerva et al. 2023; Manova et al. 2023; National Council on Prices and Reimbursement 2023; Queiroz et al. 2023; Provenzano et al. 2025; SABCS MONALEESA Update 2025; Cvetanović et al. 2026).

Baseline characteristics such as age, hormone receptor status, and ECOG performance status were broadly comparable between our cohort and the pivotal RCT

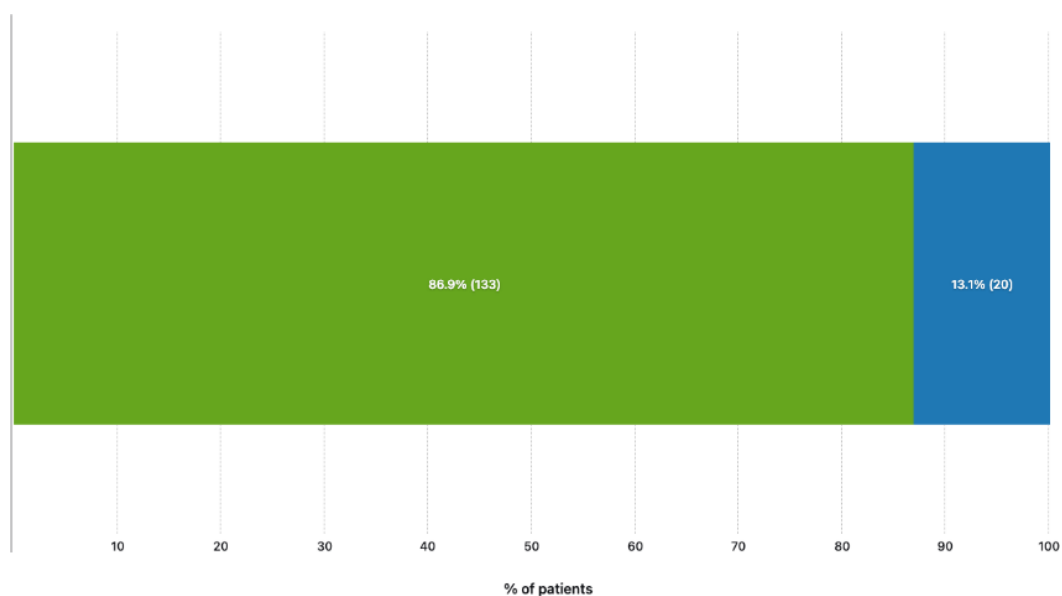


Figure 1. Clinical benefit rate of Bulgarian patients treated with ribociclib across all treatment lines in real-world clinical practice.

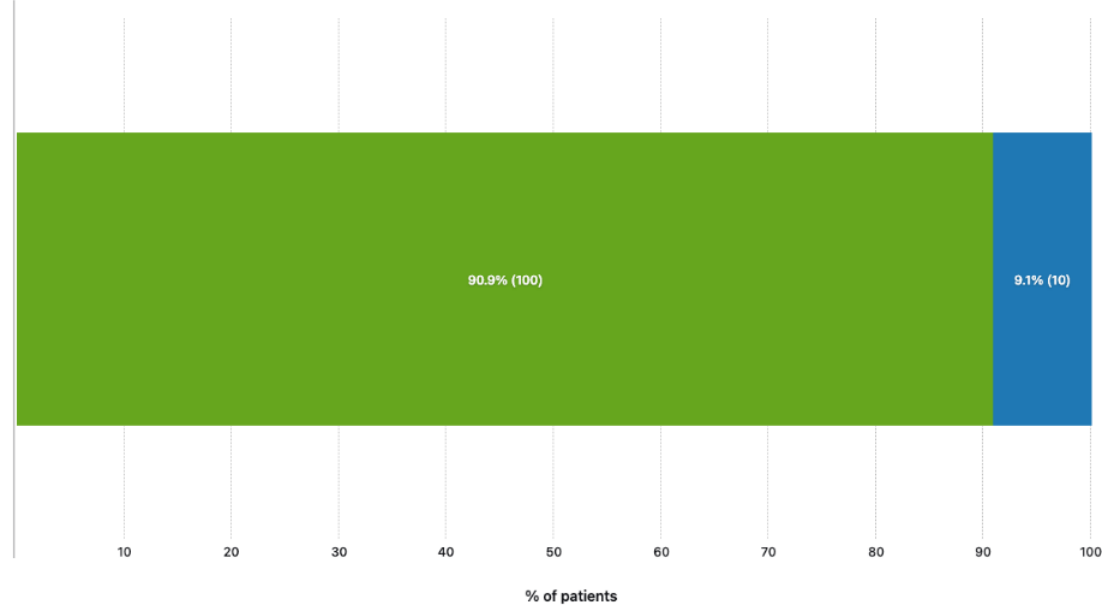


Figure 2. Clinical benefit rate of Bulgarian patients receiving first-line ribociclib in real-world clinical practice.

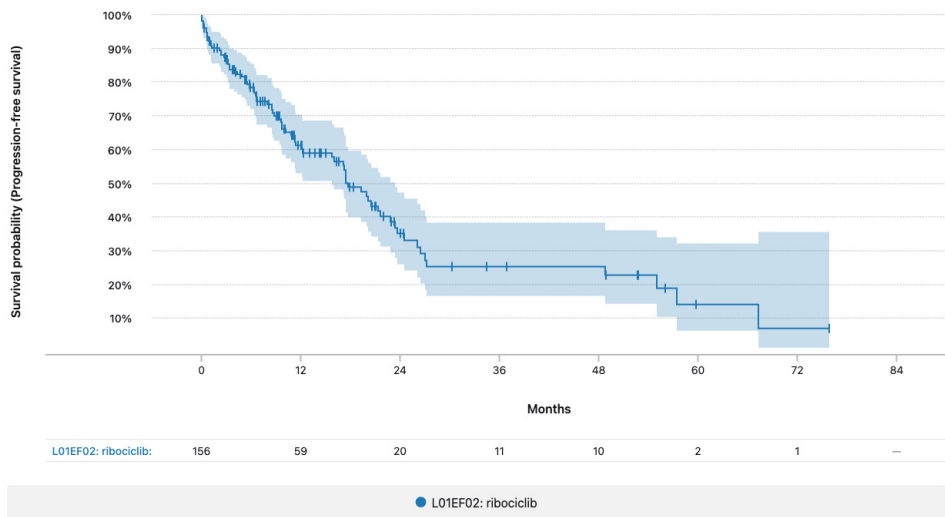


Figure 3. Progression-free survival of Bulgarian patients treated with ribociclib across all treatment lines in real-world clinical practice.

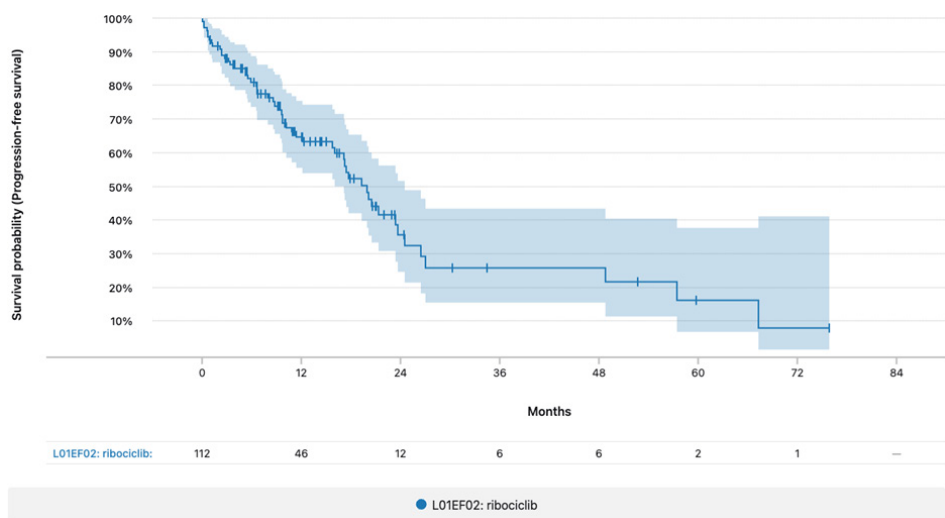


Figure 4. Progression-free survival of the Bulgarian patients on first-line ribociclib in real-world clinical practice.

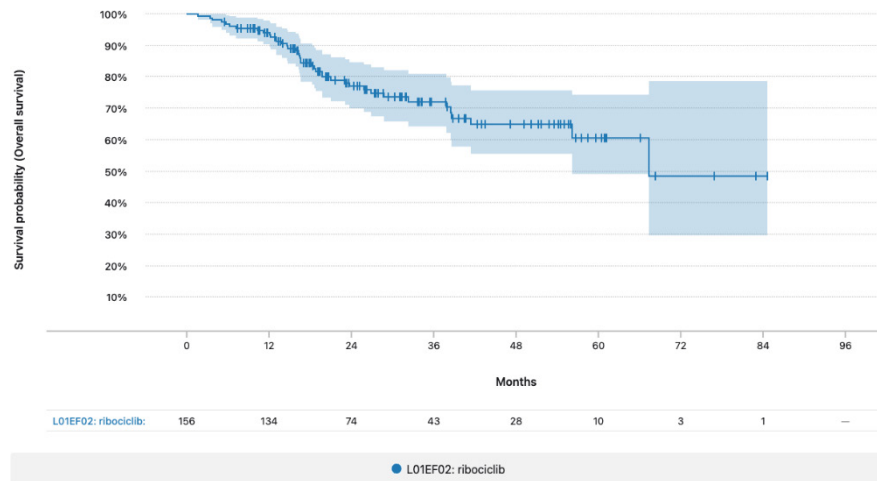


Figure 5. Overall survival of the Bulgarian patients treated with ribociclib across all treatment lines in real-world clinical practice.

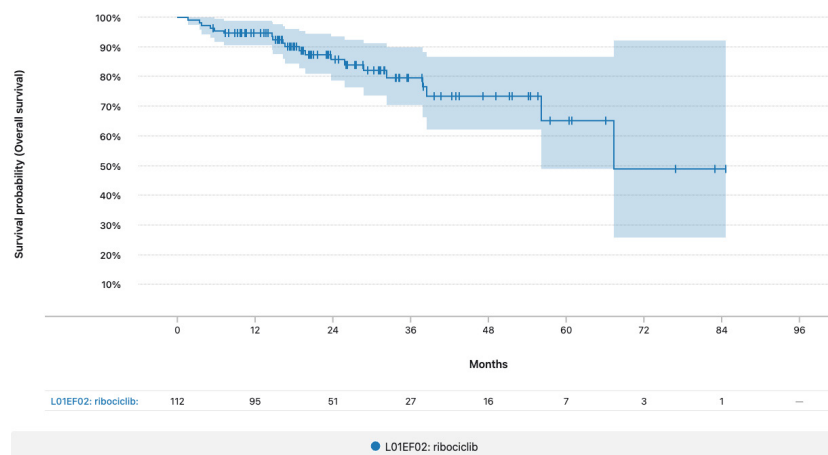


Figure 6. Overall survival of the Bulgarian patients receiving first-line ribociclib in real-world clinical practice.

Table 3. Progression-free survival of the Bulgarian patients treated with ribociclib across all treatment lines in real-world clinical practice.

Number of patients	Number of events	Median survival	3-month survival	6-month survival	12-month survival	18-month survival	24-month survival	36-month survival
156	78	17.7 months (15.8–23.4)	87% (81–92)	79% (72–86)	61% (53–71)	49% (40–60)	35% (26–47)	25% (17–38)

Table 4. Progression-free survival of the Bulgarian patients on first-line ribociclib in real-world clinical practice.

Number of patients	Number of events	Median survival	3-month survival	6-month survival	12-month survival	18-month survival	24-month survival	36-month survival
112	53	19.9 months (17.1–24.5)	88% (82–94)	81% (74–89)	65% (56–76)	52% (42–65)	36% (25–52)	26% (15–44)

Table 5. Overall survival of the Bulgarian patients treated with ribociclib across all treatment lines in real-world clinical practice.

Number of patients	Number of events	Median survival	3-month survival	6-month survival	12-month survival	18-month survival	24-month survival	36-month survival
156	40	67.3 months (56.1–N/A)	99% (98–100)	97% (94–100)	94% (90–98)	84% (78–91)	77% (70–85)	72% (64–81)

Table 6. Overall survival of the Bulgarian patients receiving first-line ribociclib in real-world clinical practice.

Number of patients	Number of events	Median survival	3-month survival	6-month survival	12-month survival	18-month survival	24-month survival	36-month survival
112	20	67.3 months (56.1–N/A)	99% (97–100)	96% (92–99)	95% (91–99)	90% (85–96)	86% (79–94)	80% (71–90)

populations. However, the proportion of patients with ECOG 0 was clearly higher in our single-center series. In everyday practice, many of these patients were discussed in a multidisciplinary tumor board before starting ribociclib, and this may have contributed to the careful selection of fitter individuals. This slightly more favorable baseline profile likely played a role in the survival outcomes we observed.

When we compared OS and PFS with the MONALEESA trials, several patterns emerged. Median OS in our cohort was 67.3 months (95% CI: 56.1–not reached), which is similar to, or numerically higher than, the median OS reported in MONALEESA-2 (63.9 months) and MONALEESA-3 (53.7 months) (Hortobagyi et al. 2016; Slamon et al. 2018). In contrast, median PFS for first-line therapy in our real-world cohort was 19.9 months (95% CI: 17.1–24.5 months). This is somewhat shorter than the 25.3 months reported in MONALEESA-2 but close to the 20.5 months observed in MONALEESA-3 (Hortobagyi et al. 2018; Tripathy et al. 2018). Overall, these findings suggest that long-term survival with ribociclib in Bulgarian clinical practice can match the level achieved in controlled trials, even though PFS appears slightly shorter. Differences in imaging intervals, documentation, and classification of progression, as well as the inclusion of patients with comorbidities or more complex disease biology, are all plausible contributors.

Several real-world evidence studies from Spain, Brazil, Italy, Greece, and Serbia have evaluated ribociclib in combination with AIs or fulvestrant in women with HR+/HER2– advanced or metastatic breast cancer (Fountzilas et al. 2020; García-Trevijano Cabetas et al. 2021; Fernández-Cuerva et al. 2023; Queiroz et al. 2023, 2023; Provenzano et al. 2025; Cvetanović et al. 2026). Despite differences in sample size, follow-up, and healthcare context, these studies consistently show that ribociclib is effective in routine care, although reported PFS and OS vary.

In Spain, Fernández-Cuerva et al. (2023) analyzed 53 patients with HR+/HER2-negative metastatic breast cancer and reported a median PFS of 27.3 months (95% CI: 20.8–71.8 months) overall and 28 months (95% CI: 15–41 months) in the first-line setting; OS was not assessed. García Trevijano Cabetas et al. (2021) studied 28 patients receiving ribociclib, mostly in first-line therapy (67.9%). They observed a 12-month PFS rate of 78.6%, with the median PFS not reached at the time of analysis, indicating durable disease control. These Spanish cohorts illustrate that, under certain conditions, PFS with ribociclib can be quite prolonged.

The Brazilian BrasiLEEira study retrospectively examined 76 patients treated with first-line CDK4/6 inhibitors, including 42 who received ribociclib (Queiroz et al. 2023). In this subgroup, the CBR was 95.2%, and median PFS was 28.0 months (95% CI: 13.1–42.9 months), which is longer than the 19.9-month median PFS in our first-line cohort, although OS was not reported. These findings highlight that real-world outcomes can be at least as good as those seen in trials but also remind us that cross-study comparisons must be interpreted with care.

The Italian PALMARES-2 study compared palbociclib, ribociclib, and abemaciclib as first-line treatment combined with endocrine therapy in HR+/HER2-negative advanced breast cancer (Provenzano et al. 2025). Among patients treated with ribociclib, median PFS was 34.1 months (IQR 13.9–86.3 months), clearly longer than in our cohort, whereas median OS was similar (65.9 months, IQR 36.7–not reached vs. 67.3 months, 95% CI: 56.1–not reached). Clinical benefit rate was not reported. Differences in patient selection, metastatic burden, and follow-up intensity may all contribute to the longer PFS. However, the comparable OS underscores the robustness of ribociclib's long-term benefit across health systems.

Real-world data from Greece and Serbia provide additional regional context. Fountzilas et al. (2020) reported outcomes for 365 women with HR+/HER2-negative advanced breast cancer treated with a CDK4/6 inhibitor plus endocrine therapy. First-line treatment yielded the longest median PFS (18.7 months), with shorter durations in the second- and third-line settings (12.0 and 7.4 months, respectively). This pattern aligns with our findings and supports early use of CDK4/6 inhibitors. A Serbian study of 132 patients treated with first-line ribociclib plus an aromatase inhibitor reported a median PFS of 30 months and a CBR of 89.3% (Cvetanović et al. 2026). Although PFS was longer than in our Bulgarian first-line cohort, the CBR was very similar to 90.9% in our cohort, suggesting that high rates of disease control with ribociclib are reproducible across neighboring countries.

Within Bulgaria, our results complement the nationwide analysis by Manova et al. (2023), which provides a broad overview of ribociclib outcomes across all centers. That study showed that ribociclib was effective in an unselected national cohort. Our single-center data suggest that when a higher proportion of patients have ECOG 0 and treatment is introduced early, clinical benefit and OS can be further optimized. In practical terms, this points to the importance of careful patient selection, multidisciplinary decision-making, and timely initiation of therapy. Taken together, the national and international real-world evidence support the effectiveness of ribociclib in routine clinical practice. The benefits seen in randomized trials can largely be reproduced outside the trial setting, particularly when ribociclib is offered early and to patients with good performance status.

Conclusion

Our retrospective study provides important real-world evidence on the use of ribociclib in combination with an aromatase inhibitor or fulvestrant for patients with HR+/HER2-negative advanced breast cancer treated in routine clinical practice in Bulgaria. The data from a single specialized oncology hospital show high clinical benefit rates and prolonged progression-free and overall survival, broadly in line with pivotal MONALEESA trials and with international and national real-world studies, including the nationwide analysis by Manova et al. (2023). Within the Bulgarian

context, our results suggest that when ribociclib is introduced early and offered predominantly to patients with good performance status, outcomes can match or numerically exceed those observed in broader national cohorts. This implies that optimizing patient selection and management may translate into additional clinical benefit for Bulgarian patients.

Although its retrospective design and single-center setting limit the study, it complements existing nationwide data. It helps bridge the gap between randomized controlled trials and everyday clinical practice in Bulgaria. Overall, the accumulating Bulgarian and international evidence supports ribociclib-based endocrine therapy as a key component of systemic treatment for HR+/HER2-negative advanced breast cancer and underscores its value as a therapeutic option capable of delivering meaningful survival gains in real-world care.

Additional information

Conflict of interest

The authors declare no commercial or financial conflicts of interest.

Ethical statements

The authors declared that no clinical trials were used in the present study.

The authors declared that no experiments on humans or human tissues were performed for the present study.

The study used anonymized, retrospective electronic health records collected via hospital-integrated software. According to

local Bulgarian regulations, ethics committee approval and patient informed consent were not required for this type of research.

The authors declared that no experiments on animals were performed for the present study.

The authors declared that no commercially available immortalised human and animal cell lines were used in the present study.

Use of AI

The authors accept full responsibility for the content of the manuscript, including the disclosure of any use of AI. No AI tools were used in the preparation of this manuscript.

Funding

This study is financed by the European Union-NextGenerationEU through the National Recovery and Resilience Plan of the Republic of Bulgaria, project № BG-RRP-2.004-0004-C01.

Author contributions

All authors have contributed equally.

Author ORCIDs

Mariyana Eneva  <https://orcid.org/0009-0007-7853-9793>

Petya Borisova  <https://orcid.org/0009-0003-2096-7681>

Boryana Ivanova  <https://orcid.org/0000-0003-2466-9254>

Alexandra Savova  <https://orcid.org/0000-0003-4579-5524>

Manoela Manova  <https://orcid.org/0000-0002-8749-7974>

Data availability

Qualified researchers may obtain data from this study from the corresponding author upon reasonable request.

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