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Original Article

Optimizing abemaciclib-induced diarrhea management in patients with breast cancer: a pragmatic 2-group study using a postbiotic microbiota stabilizer

Rita De Sanctis[*,1,2], Paola Tiberio[2], Flavia Jacobs[1,2], Mariangela Gaudio[1,2], Chiara Benvenuti[1,2], Laura Giordano[3], Rosalba Torrisi[2], Alberto Zambelli[1,2], Chiara Pozzi[2], Giuseppe Penna[2], Armando Santoro[1,2], Maria Rescigno[1,2]

[1]Department of Biomedical Sciences, Humanitas University, 20072 Pieve Emanuele, Milan, Italy
[2]Medical Oncology and Hematology Unit, IRCCS Humanitas Research Hospital, 20089 Rozzano, Milan, Italy
[3]Biostatistic Unit, IRCCS Humanitas Research Hospital, 20089 Rozzano, Milan, Italy

[*]Corresponding author: Rita De Sanctis, Medical Oncology and Hematology Unit, IRCCS Humanitas Research Hospital, Via A. Manzoni 56, 20089 Rozzano, Milan, Italy (rita.de_sanctis@hunimed.eu).

Abstract

Background: Abemaciclib-induced diarrhea is a relevant concern in clinical practice. Postbiotics have emerged as a promising option for managing it.

Materials and Methods: We conducted a retrospective-prospective, 2-group, observational study to assess the impact of the postbiotic PostbiotiX-Restore, derived by *Lactobacillus paracasei* CNCM I-5220, on abemaciclib-induced diarrhea in patients with hormone receptor-positive HER2-negative breast cancer. The prospective population (Postbio group) received postbiotic during the first cycle of abemaciclib, while the retrospective one received standard care (Standard group). Diarrhea grading was defined according to the National Cancer Institute's Common Terminology Criteria for Adverse Events.

Results: During the first cycle, diarrhea occurred in 78.9% of patients in the Standard cohort and 97.1% in the Postbio one, with most cases being G1-G2. Severe (G3) diarrhea was significantly less frequent in the Postbio group (0%) compared to the Standard one (7.9%; $P = .029$). Over the entire study period, while the grading difference was not statistically significant, G3 events were less frequent in the Postbio population (5.9%) than the Standard one (15.4%). Moreover, Postbio patients required fewer dose reductions due to diarrhea compared to the Standard group ($P = .002$). Notably, in the Postbio population, G1 and G2 events had short median durations (3 and 1 days, respectively) and, for the 2 patients experiencing G3 events during the second abemaciclib cycle (off postbiotic), diarrhea lasted only 1 day.

Conclusions: Our study demonstrates the effect of PostbiotiX-Restore in mitigating abemaciclib-induced diarrhea, resulting in reduced severity, fewer dose reductions, and shorter duration. Further exploration and validation in larger cohorts are needed.

Key words: CDK4/6 inhibitors; patient-reported outcome; *Lactobacillus paracasei* CNCM I-5220; quality of life; diarrhea; microbiota.

Implications for Practice

The incidence and severity of abemaciclib-induced gastrointestinal events are a relevant concern in clinical practice. By educating patients about expected toxicities and their management, we can potentially enhance compliance, allowing patients to continue treatment without early discontinuations that may compromise its effectiveness. In line with this hypothesis, the reduced severity of gastrointestinal toxicity in the Postbio group translated into a reduced need for dose reduction, temporary suspension, or permanent discontinuation of abemaciclib therapy. Thus, our findings provide valuable insights into the potential benefits of PostbiotiX-Restore in mitigating abemaciclib-induced diarrhea, which may have broad implications for the management of oncology treatments.

Introduction

Abemaciclib, a cyclin-dependent kinase 4 and 6 inhibitor (CDK4/6i), is approved for treating hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2–) advanced breast cancer (BC), in both endocrine-sensitive and resistant settings, based on the results of the MONARCH-3 and MONARCH-2 trials,[1,2] and high-risk HR+/HER2– early BC, following the significant invasive-disease free survival (iDFS) data reported in the MONARCH-E trial.[3]

The most common adverse event (AE) of abemaciclib is diarrhea, which has a significant impact on health-related quality of life (HRQoL).[4,5] Its incidence, characteristics, and impact on treatment adherence and outcomes were overall

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consistent in advanced and early settings.[6,7] Specifically, 84.6% and 83.5% of patients experienced diarrhea in advanced and early disease trials, respectively, with grade (G) ≥3 reported for 11.7% (no occurrence of G4 or G5) and 7.8% (all G3 except one case of G5) of patients.[6,7]

The role of the microbiome in gastrointestinal manifestations is gaining significance, with many researches focusing on postbiotics, which are functional bioactive compounds derived from probiotic microorganisms. Postbiotics regulate host-microbe interaction and improve intestinal homeostasis by promoting a healthier gut environment and protecting the mucosal barrier from pathogenic invasion.[8-10]

This study aims to evaluate the effect of the PostbiotiX-Restore (henceforth called postbiotic), a new postbiotic-based food supplement containing a fermented Fructo-OligoSaccharide (FOS) by *Lactobacillus paracasei* CNCM I-5220, on abemaciclib-induced diarrhea by comparing gastrointestinal toxicities in patients receiving the food supplement (prospective study) with those in women treated according to standard care (retrospective group). Despite acknowledging its mixed nature, our pragmatic retrospective-prospective observational study was designed to evaluate the effectiveness of postbiotic administration in a real-world setting, thus maximizing the applicability and generalizability of this approach, especially in its early phase of assessment.

Materials and methods

Study design and participants

This observational study compared 2 populations: a prospective (Postbio group) and a retrospective cohort (Standard group). The Postbio group enrolled patients between January 2022 and January 2023, while the Standard group included patients treated from July 2019 to May 2021.[11] All patients received abemaciclib at the standard dose of 150 mg orally twice daily in combination with endocrine therapy (ET) at IRCCS Humanitas Research Hospital in Rozzano, Italy. Depending on the endocrine sensitivity of the patients and the adjuvant/metastatic setting, ET consisted of an aromatase inhibitor (letrozole, anastrozole, or exemestane) taken orally once daily, or fulvestrant at 500 mg administered intramuscularly on days 1, 14, and 28 for the first cycle, and then every 28 days. Luteinizing hormone-releasing hormone (LHRH) analog was administered to premenopausal patients. Abemaciclib plus ET was continued until disease progression or the occurrence of unacceptable toxicities in metastatic BC, and for 2 years in case of early-stage disease.

For the prospective group, inclusion criteria were

(a) advanced (locoregionally recurrent or metastatic) HR+/HER2− BC not amenable to curative therapy, or high-risk early BC (ie, pN2 or pN1 with a tumor size ≥5 cm, and/or a histologic grade of 3, and/or a proliferative index ki-67 ≥20%);
(b) Eastern Cooperative Oncology Group Performance Status (ECOG PS) ≤2; and
(c) a washout period of at least 21 days between the last adjuvant or first-line ET dose, if any.

The exclusion criteria were

(a) use of immunomodulatory agents (including steroid) at the time of or in the 2 months before enrollment;
(b) use of antibiotics or probiotics at the time of or during the month before enrollment;
(c) inflammatory bowel disease;
(d) history of major surgical resection involving the stomach or small bowel; and
(e) patient currently receiving strong inducers or inhibitors of Cytochrome P450 (CYP) 3A4/5, or drugs metabolized through CYP3A4/5 that cannot be discontinued 14 days prior to starting abemaciclib.

For the retrospective cohort, inclusion and exclusion criteria have been reported elsewhere.[11]

For both groups, patients with a follow-up of less than 1 month and/or unavailable safety data were excluded.

In the prospective group, data were gathered using ad hoc case report forms. Specifically, women in the Postbio group fulfilled a survey about evacuation frequency and consistency and eating habits at baseline. Additionally, during the first 2 cycles of abemaciclib, patients completed a web-based, self-administered, daily questionnaire on bowel movements, concomitant medications, diet, and treatment discontinuation (Supplementary Figure S1 shows the baseline questionnaire, and Supplementary Figure S2 shows the daily questionnaire), and the Functional Assessment of Cancer Therapy-Breast (FACT-B) questionnaire (at baseline and after the first and second cycle of abemaciclib).[12,13] Whereas, in the retrospective population, data were extracted from patients' medical records. In fact, during routine visits, patients were asked to report any AE they experienced during abemaciclib treatment, especially diarrhea, given its significance as a specific adverse event associated with this CDK4/6 inhibitor,[14] potentially leading to dose reduction or treatment discontinuation.

Diarrhea events were assessed by comparing the number of bowel movements over baseline, following the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE).[15]

Patients in the Postbio group received a prophylaxis treatment with the postbiotic food supplement from day −7 to +28 (ie, the end of the first cycle of abemaciclib; Figure 1). Each sachet (2 g) of postbiotic contains 200 mg of fermented FOS by *Lactobacillus paracasei*. If diarrhea occurred, all patients in both cohorts were advised to follow guideline-based treatment with loperamide.[7,16,17] Abemaciclib dose reduction and treatment discontinuation were managed as per label indication.

The study was approved by the IRCCS Humanitas Research Hospital Ethics Committee (Protocol identifying number ONC/OSS-19/2021). All patients signed the informed consent form, in accordance with the Declaration of Helsinki.

Study objectives

The primary objective was to evaluate the effect of the postbiotic on abemaciclib-induced diarrhea by comparing its severity in patients receiving the food supplement versus those treated with standard care.

Secondary objectives included analyzing the postbiotic's impact on treatment adherence (by comparing dose reduction and treatment interruption/discontinuation due to diarrhea between the 2 groups), median duration of diarrhea, patients' HRQoL, and non-diarrhea AEs during abemaciclib treatment.

Statistical analysis

Data were analyzed through descriptive statistics. The median duration of diarrhea was calculated only for cases experiencing the event. Univariate statistical analysis was performed using contingency tables, chi-squared, Fisher's exact, and Mann-Whitney tests. A paired *t*-test was used to assess differences in FACT-B scores.

All *P*-values were 2-sided, and statistical significance was set at $P < .05$. Analyses were performed with SAS version 9.4 and STATA version 15.

Results

Patient characteristics

Seventy-three women with HR+/HER2– BC eligible for treatment with abemaciclib plus ET were enrolled in the 2 studies (34 in the Postbio group, 39 in the Standard one).[11] Figure 2 reports the CONSORT Diagram showing participant flow. Table 1 shows the clinical demographics of the 2 populations. Of note, there were no significant differences between groups at baseline, except for disease stage. Consistently, there was a difference in the ET (higher number of patients on fulvestrant in the Standard cohort) due to the inclusion of patients with early BC in the Postbio group.

Gastrointestinal toxicity

During the first cycle of abemaciclib treatment, as reported in Table 2, diarrhea was observed in 78.9% of patients in the Standard group and 97.1% of the Postbio women. In both groups, the majority of patients experienced G1 diarrhea and, in the Postbio population, no cases of G3 diarrhea were reported (Table 2). The difference in grading between the 2 groups was statistically significant ($P = .029$).

Considering the entire observation period, 92.3% of patients in the Standard cohort and 100% in the Postbio group reported diarrhea of any grade.[11] The number of patients experiencing G3 events was higher than in the first cycle, but still lower in the Postbio group (5.9%) compared to the Standard one (15.4%; Table 2).

Two patients with G3 diarrhea in the Postbio group had both undergone adjuvant chemotherapies before starting abemaciclib. However, there were no significant differences in diarrhea severity when comparing patients who had recently received chemotherapy or not ($P = .51$).

In addition, the Postbio cohort showed a short median duration for G1 and G2 events, with G1 events lasting 3 days (range 1-17 for cycle 1 and 1-15 for cycle 2) and G2 events 1 day (range 1-5 for cycle 1 and 1-3 for cycle 2). Interestingly, 2 patients experienced G3 events lasting 1 day during the second cycle of abemaciclib (off postbiotic), indicating that the postbiotic effect persisted but not enough to protect against G3 diarrhea.

Management of diarrhea and its impact on treatment modifications

During the first cycle of abemaciclib, 60% of Standard group patients used loperamide for diarrhea management, while 39.4% in the Postbio cohort used it in addition to the postbiotic. No significant differences were observed in treatment interruption/discontinuation or dose reduction due to diarrhea (Table 3).

During the entire study period, in the Standard group, 26 patients (72%) used loperamide to reduce diarrhea, while 16 patients (47.1%) required it in the Postbio group. Nevertheless, treatment changes were needed and a significant difference between the 2 groups was observed in the

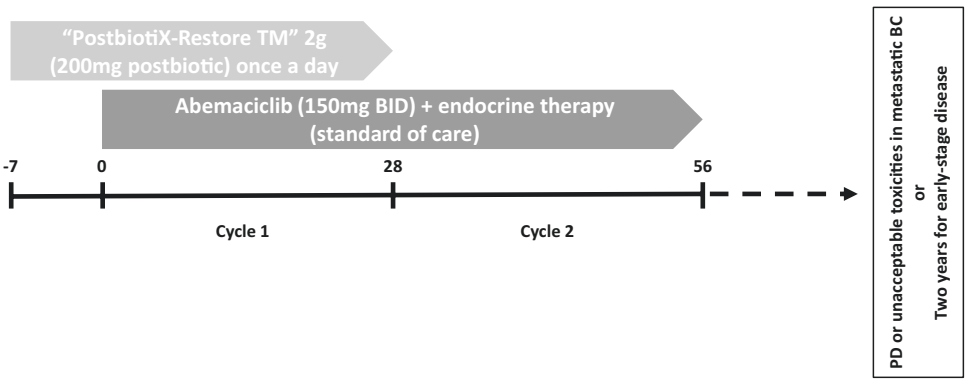

Figure 1. Treatment schedule for the Postbio group.

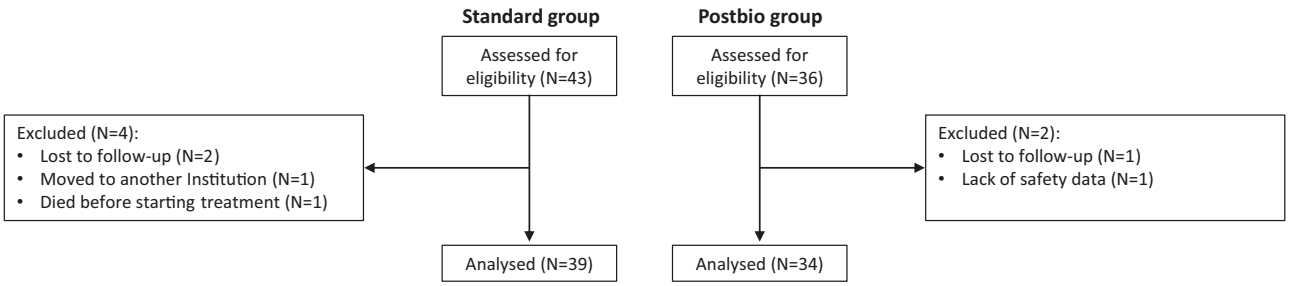

Figure 2. CONSORT Diagram showing participant flow of both groups.

Table 1. Clinical demographical characteristics of enrolled patients.

Characteristics	Overall period		
	Standard group ($N = 39$), *n* (%)	Postbio group ($N = 34$), *n* (%)	*P*-value
Age, median (range)	64 (41-82)	57 (34-79)	.084
BMI*			
≤18.5	3 (7.6)	0 (0.0)	.180
18.5-24.9	15 (38.4)	23 (67.6)	
25-29.9	7 (17.9)	5 (14.7)	
≥30	6 (15.3)	6 (17.6)	
ECOG PS			
0	21 (53.8)	27 (79.4)	.128
1	11 (28.2)	5 (14.7)	
2	6 (15.4)	2 (5.9)	
3	1 (2.6)	0 (0.0)	
Smoking status			
Yes	10 (25.6)	3 (8.8)	.073
No	29 (74.4)	31 (91.2)	
Main medical conditions			
Food allergy	1 (2.6)	2 (5.9)	.808
Erosive gastropathy	0 (0.0)	1 (2.9)	
Glucose intolerance	1 (2.6)	1 (2.9)	
Dyslipidemia	5 (12.8)	3 (8.9)	
Diabetes	1 (2.6)	1 (2.9)	
Dysthyroidism	3 (7.7)	5 (14.7)	
None of the above	28 (71.7)	21 (61.8)	
Setting			
Adjuvant	0 (0.0)	12 (35.3)	<.001
Metastatic	39 (100.0)	22 (64.7)	
Metastatic site			
Visceral only	11 (28.2)	5 (14.7)	.645
Bone only	13 (33.3)	11 (32.3)	
Visceral and bone	10 (25.6)	4 (11.8)	
Other site	5 (12.9)	2 (5.9)	
Endocrine therapy			
Anastrozole	0 (0.0)	1 (2.9)	.019
Exemestane	0 (0.0)	4 (11.8)	
Fulvestrant	20 (51.2)	8 (23.5)	
Letrozole	19 (48.7)	21 (61.8)	
LHRH analog			
Yes	8 (20.5)	11 (32.3)	.293
No	31 (79.5)	23 (67.7)	

*For 8 patients of the Standard group, BMI at the time of enrollment was not available.
Abbreviation: BMI, body mass index.

number of patients requiring dose reduction due to diarrhea ($P = .002$; Table 3).

Non-diarrhea AEs

Further AEs are reported in Table 4 for both groups.

Either during the first cycle or throughout the entire study period, non-diarrhea AEs were significantly more reported by patients in the Postbio group compared to the Standard one (Table 4).[11]

Table 2. Number of patients experiencing diarrhea of different severity (maximum grades, or G, as defined by NCI-CTCAE) in both groups throughout the first cycle of abemaciclib treatment and the entire observational period.

G max	Cycle 1			Overall period		
	Standard group, *n* (%)	Postbio group, *n* (%)	*P*-value	Standard group, *n* (%)	Postbio group, *n* (%)	*P*-value
0	8 (21.1)	1 (2.9)	.029	3 (7.7)	0 (0.0)	.169
1	20 (52.6)	23 (67.6)		18 (46.2)	17 (50.0)	
2	7 (18.4)	10 (29.4)		12 (30.8)	15 (44.1)	
3	3 (7.9)	0 (0.0)		6 (15.4)	2 (5.9)	

In addition, in the Standard population, 2 patients experienced constipation due to loperamide treatment,[11] whereas in the Postbio group, no women reported this AE.

Health-related quality of life

The Postbio cohort's HRQoL data (data available for 27 patients) showed a median FACT-B composite score of 103 (interquartile range [IQR]: 87-115) at baseline, with a mean change of 0.46 points from baseline to the first abemaciclib cycle (95% CI, −4.10 to 5.03). No significant difference was found between the baseline and 1 month scores ($P = .84$). A limited number of patients completed the questionnaire at the end of the observation period, thus hindering the calculation of HRQoL deterioration after the first cycle.

Discussion

Our study aimed to demonstrate the efficacy of PostbiotiX-Restore in optimizing the management of abemaciclib-induced diarrhea. Postbiotics can protect the mucosal barrier by preserving the expression of mucin-2 and of Zonula occludens-1 which allows to seal the epithelial barrier and to avoid bacterial translocation.[9]

The most relevant outcome was the absence of severe diarrhea in the Postbio group during the first month of abemaciclib therapy in combination with the postbiotic, in contrast to the Standard one. However, this did not translate into a lower incidence of G1/2 toxicities, and the number of patients without diarrhea events was lower in the Postbio population. Thus, we can hypothesize a gastrointestinal interaction between abemaciclib and the postbiotic that warrants further translational investigation. Indeed, over 81% of abemaciclib is excreted through feces as active metabolites, which significantly contributes to diarrhea development. Furthermore, abemaciclib affects CDK9, a crucial regulator of intestinal cell growth.[18] The observed reduction of G3 toxicity and increase in the rate with G2, meaning those patients who were in the Postbiotic group would have G3 conversion to a G2, may raise questions about the influence of coaching or other external factors during the prospective study. While we acknowledge the possibility of a greater patients' awareness contributing to these outcomes, we believe that the mechanism of action of postbiotics, particularly in modulating gut microbiota and low-grade inflammation, may have played a role in downgrading the severity of diarrhea toxicity. Furthermore, stringent monitoring protocols were implemented to ensure uniformity in data collection and minimize potential biases. In addition, due to the well-known safety

Table 3. Treatment discontinuation and dose reduction in Standard and Postbio groups during the first cycle of abemaciclib treatment and the entire observational period.

	Cycle 1			Overall period		
	Standard group, *n* (%)	Postbio group, *n* (%)	*P*-value	Standard group, *n* (%)	Postbio group, *n* (%)	*P*-value
Temporary treatment interruption	4 (10.3)	0 (0.0)	.118	6 (15.4)	1 (2.9)	.113
Permanent treatment discontinuation	3 (7.7)	0 (0.0)	.243	4 (10.3)	0 (0.0)	.118
Dose reduction	5 (12.8)	0 (0.0)	.057	12 (30.8)	1 (2.9)	.002

Table 4. AEs other than gastrointestinal toxicity experienced by the 2 populations during the first cycle and the overall abemaciclib treatment.

	Cycle 1			Overall period		
	Standard group, *n* (%)	Postbio group, *n* (%)	*P*-value	Standard group, *n* (%)	Postbio group, *n* (%)	*P*-value
Nausea/vomiting	10 (25.6)	19 (55.9)	.016	11 (28.2)	21 (61.8)	.005
Fatigue	6 (15.4)	22 (64.7)	<.001	13 (33.3)	24 (70.6)	.002
Abdominal pain	5 (12.8)	21 (61.8)	<.001	8 (20.5)	23 (67.6)	<.001

profile of abemaciclib, at every routine visit, patients with BC in the Standard group were regularly prompted to report any AEs experienced since their last visit, with their symptoms and respective grades being accurately documented in an electronic medical record. Despite the lower incidence of severe diarrhea events in the Postbio group, it is important to note that G1/2 diarrhea events showed a relatively short duration, suggesting the postbiotic as an effective management strategy.

Moreover, the reduced severity of diarrhea in the Postbio group translated into the possibility of administering abemaciclib with a diminished need for dose reduction, temporary suspension, or permanent discontinuation. Alternatively, nowadays it is possible to maintain a patient on a CDK4/6i-based treatment by the utilization of alternative CDK4/6 inhibitors that are devoid of dose-limiting AEs (ie, diarrhea in the case of abemaciclib), such as ribociclib or palbociclib.[19-21] In the absence of effective preventive or management strategies of diarrhea, the switch to another CDK4/6i could be considered as a strategy to mitigate the incidence of diarrhea toxicity in patients undergoing this type of treatment.

The study design implemented postbiotic administration solely during the first month of abemaciclib therapy in the prospective population, guided by literature data indicating a higher incidence and severity of diarrhea at abemaciclib initiation.[4-7] However, it is essential to recognize that chronic toxicities, even at G1/2, can have significant implications if sustained over a prolonged period. While our study focused on short-term outcomes, the potential impact of chronic toxicities warrants consideration in future investigations with longer follow-up periods and/or longer postbiotic administration to assess the durability of treatment effects and mitigate potential long-term consequences. It is also noteworthy that the postbiotic was administered alongside standard supportive therapy with loperamide, which could potentially introduce a confounding effect but it was necessary according to good clinical practice. When evaluating loperamide use, we found that fewer Postbio patients required it. Furthermore, despite guideline recommendations, loperamide was associated with other AEs, including moderate/severe constipation (as known by the neoMONARCH study).[22]

Additionally, in the Postbio population, daily questionnaires allowed for the assessment of diarrhea duration, a critical factor affecting HRQoL. Nevertheless, a direct comparison of diarrhea duration between the 2 groups was not feasible due to the retrospective data collection for the Standard group. In early and advanced setting studies (eg, MONARCH-E, MONARCH-1, and MONARCH-3 trials), the median duration ranged from 5 to 10.5 days and from 4.5 to 8 days for G2 and G3 events, respectively.[5-7,23] Here, Postbio patients had considerably shorter median durations, which were 1 day for both G2 and G3 (range 1-5 and 1-1, respectively). While acknowledging the limitations of comparing populations with different sample sizes and the lack of statistical significance, the clinical implication of shorter duration for moderate to severe gastrointestinal events is notable when using postbiotic and could translate into better patients' HRQoL. Consistently, in the Postbio group, the overall change in the FACT-B score from baseline to the end of the first abemaciclib cycle did not reveal a significant difference.

We also observed a higher incidence of non-diarrhea AEs (fatigue, nausea or vomiting, and abdominal pain) in the Postbio population compared to the Standard one. We believe that this observation is not indicative of a true higher incidence of such events but rather related to a sort of reverse recall bias. Indeed, all Postbio patients were asked to complete a daily questionnaire regarding all symptoms experienced, in addition to bowel movements. In contrast, information for the retrospective cohort was gathered from medical records where there may have been underreporting of less impacting AEs (or at least those assessed as such by the physician and/or patient during the visits). Similarly, we could speculate that diarrhea events reported by Postbio patients may be more stringent than what assessed during routine visits in the Standard group. The present study confirms that PROs provide valuable insights, and that they should be integrated with clinician assessment.[24,25]

A recent randomized phase II study (MERMAID, WJOG11318B) examined the use of probiotic *Bifidobacterium* in 2 arms: one with *Bifidobacterium* alone (Arm A) and the other with both *Bifidobacterium* and trimebutine maleate (Arm B) over a 28-day observation period.[26] In comparison to our study, Postbio patients reported a lower incidence of G2 and G3 events in the first cycle (29.4% G2 and no G3 events vs 52% and 50% G2 in Arm A and B, respectively, and one patient in each arm for G3), shorter median duration of G2 diarrhea (1 day in our study vs 2-2.5 days in the MERMAID one), and lower treatment changes due to diarrhea (no treatment modifications vs 5.7%). Notably, one advantage of the posbiotic over probiotics is the absence of any form of bacteria either dead or alive, making the postbiotic treatment very safe.

Our study has some limitations that should be taken into account. First, the mixed retrospective-prospective design poses challenges primarily rooted in different data collection methods between the 2 cohorts. In particular, retrospective data collection relies on patient recollection, which may introduce recall bias, inaccuracies, and a higher number of missing data compared to prospectively collected data. Moreover, the inclusion of patients in the retrospective cohort based on the availability of historical records rather than predefined study criteria could also introduce selection bias. Nonetheless, the retrospective cohort, previously reported elsewhere,[11] included all consecutive patients with HR+/HER2– advanced BC treated with abemaciclib and endocrine therapy and obtained through an electronic database thus avoiding a selective reporting of outcomes. Second, the limited sample size restricts the generalizability of our findings to a broader population. Finally, the potential influence of uncontrolled variables and confounders—especially in the Standard population—cannot be completely ruled out. These inherent limitations highlight the importance of cautious interpretation of the findings. Despite these limitations, our work has various strengths: it represents a real-world investigation carried out in 2 uniform groups of patients receiving abemaciclib plus ET at a single medical center. The mixed nature of the research allows a better evaluation of the postbiotic's effect on mitigating CDK4/6i-induced diarrhea. Comparing the Postbio cohort to a control group without additional gastrointestinal interventions is another strength of the study. Furthermore, although the mixed study design did not involve randomization, the Postbio and Standard populations did not exhibit significant differences. Finally, in the Postbio group, safety data and treatment adherence were comprehensively documented through online questionnaires, allowing for accurate evaluation of diarrhea based on NCI-CTCAE and providing real knowledge of patients' status without recall bias during routine visits.[17]

Conclusions

In conclusion, our study sheds light on the potential benefits of PostbiotiX-Restore in managing abemaciclib-induced diarrhea, which could have implications for treatment adherence, efficacy, and patients' quality of life. However, given the preliminary nature of these findings, further research is warranted to confirm these findings and explore their broader clinical implications.

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Author contributions

Rita De Sanctis: Conception and design, Provision of study material or patients, Collection and/or assembly of data, Data analysis and interpretation, Manuscript writing, Final approval of manuscript. Paola Tiberio: Conception and design, Collection and/or assembly of data, Data analysis and interpretation, Manuscript writing, Final approval of manuscript. Flavia Jacobs: Provision of study material or patients, Collection and/or assembly of data, Data analysis and interpretation, Final approval of manuscript. Mariangela Gaudio: Provision of study material or patients, Final approval of manuscript. Chiara Benvenuti: Provision of study material or patients, Final approval of manuscript. Laura Giordano: Data analysis and interpretation, Final approval of manuscript. Rosalba Torrisi: Provision of study material or patients, Final approval of manuscript. Alberto Zambelli: Provision of study material or patients, Final approval of manuscript. Chiara Pozzi: Conception and design, Final approval of manuscript. Giuseppe Penna: Final approval of manuscript. Armando Santoro: Conception and design, Final approval of manuscript. Maria Rescigno: Conception and design, Final approval of manuscript. Armando Santoro and Maria Rescigno contributed equally.

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Conflicts of interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests. A.S.: Advisory Board: Bristol-Myers Squibb (BMS), Servier, Gilead, Pfizer, Eisai, Bayer, Merck Sharp & Dohme (MSD). Consultancy: Arqule, Sanofi, Incyte. Speaker's Bureau: Takeda, BMS, Roche, Abb-Vie, Amgen, Celgene, Servier, Gilead, Astrazeneca, Pfizer, Arqule, Lilly, Sandoz, Eisai, Novartis, Bayer, MSD (all outside the present work); A.Z. has received personal fees and non-financial support from Novartis, AstraZeneca, Lilly, Pfizer, Daiichi Sankyo, MDS Merck Sharp&Dome, Roche, Seagen, Exact Sciences, Gilead, Istituto Gentili (all outside the present work); R.T. has received funding from Astra Zeneca, Pfizer, Eli Lilly, Exact Sciences and MSD (all outside the present work); R.D.S. honoraria for advisory board consultancy from Novartis, Istituto Clinico Gentili, Amgen, EISAI, Lilly and Gilead (all outside the present work); G.P. and M.R. are founders of Postbiotica S.r.l.; M.R. is chief scientific officer of Postbiotica. The other authors declare no competing interests.

Data availability

The data presented in this study are available on reasonable request from the corresponding author.

Supplementary material

Supplementary material is available at *The Oncologist* online.

References

1. Goetz MP, Toi M, Campone M, et al. MONARCH 3: abemaciclib as initial therapy for advanced breast cancer. *J Clin Oncol*. 2017;35(32):3638-3646. https://doi.org/10.1200/JCO.2017.75.6155
2. Sledge GW Jr, Toi M, Neven P, et al. MONARCH 2: abemaciclib in combination with fulvestrant in women with HR+/HER2-advanced breast cancer who had progressed while receiving endocrine therapy. *J Clin Oncol*. 2017;35(25):2875-2884. https://doi.org/10.1200/JCO.2017.73.7585
3. Johnston SRD, Harbeck N, Hegg R, et al.; monarchE Committee Members and Investigators. Abemaciclib combined with endocrine therapy for the adjuvant treatment of HR1, HER22, node-positive, high-risk, early breast cancer (monarchE). *J Clin Oncol*. 2020;38(34):3987-3998. https://doi.org/10.1200/JCO.20.02514
4. Kaufman PA, Toi M, Neven P, et al. Health-related quality of life in MONARCH 2: abemaciclib plus fulvestrant in hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy. *Oncologist*. 2020;25(2):e243-e251. https://doi.org/10.1634/theoncologist.2019-0551
5. Goetz MP, Martin M, Tokunaga E, et al. Health-related quality of life in MONARCH 3: abemaciclib plus an aromatase inhibitor as initial therapy in HR+, HER2– advanced breast cancer. *Oncologist*. 2020;25(9):e1346-e1354. https://doi.org/10.1634/theoncologist.2020-0084
6. Rugo HS, Huober J, García-Sáenz JA, et al. Management of abemaciclib-associated adverse events in patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: safety analysis of MONARCH 2 and MONARCH 3. *Oncologist*. 2021;26(1):e53-e65. https://doi.org/10.1002/onco.13531
7. Rugo HS, O'Shaughnessy J, Boyle F, et al.; monarchE Committee Members. Adjuvant abemaciclib combined with endocrine therapy for high-risk early breast cancer: safety and patient-reported outcomes from the monarchE study. *Ann Oncol*. 2022;33(6):616-627. https://doi.org/10.1016/j.annonc.2022.03.006
8. Tsilingiri K, Rescigno M. Postbiotics: what else? *Benef Microbes*. 2013;4(1):101-107. https://doi.org/10.3920/BM2012.0046
9. Algieri F, Tanaskovic N, Rincon CC, et al. Lactobacillus paracasei CNCM I-5220-derived postbiotic protects from the leaky-gut. *Front Microbiol*. 2023;14:1157164. https://doi.org/10.3389/fmicb.2023.1157164
10. Ferrari V, Lo Cascio A, Melacarne A, et al. Sensitizing cancer cells to immune checkpoint inhibitors by microbiota-mediated upregulation of HLA class I. *Cancer Cell*. 2023;41(10):1717-1730.e4. https://doi.org/10.1016/j.ccell.2023.08.014
11. Jacobs F, Agostinetto E, Solferino A, et al. Sticking to the rules: outcome and success rate of guideline-based diarrhea management in metastatic breast cancer patients treated with abemaciclib. *J Clin Med*. 2023;12(5):1775. https://doi.org/10.3390/jcm12051775
12. Brady MJ, Cella DF, Mo F, et al. Reliability and validity of the functional assessment of cancer therapy-breast quality-of-life instrument. *J Clin Oncol*. 1997;15(3):974-986. https://doi.org/10.1200/JCO.1997.15.3.974
13. FACT-B Scoring Guidelines (Version 4). Accessed January 1, 2021. https://www.facit.org/measures/FACT-B
14. Pu D, Wu Y, Xu D, et al. The adverse events of CDK4/6 inhibitors for HR+/ HER2- breast cancer: an umbrella review of meta-analyses of randomized controlled trials. *Front Pharmacol*. 2024;15:1269922. https://doi.org/10.3389/fphar.2024.1269922
15. Common Terminology Criteria for Adverse Events (CTCAE). US Department of Health and Human Services, National Institutes of Health, National Cancer Institute. Accessed January 1, 2021. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_50
16. Management-of-abemaciclib-verzenio-associated-diarrhea_PQI_NCOODA.Pdf. Accessed January 1, 2021. https://www.ncoda.org/wp-content/uploads/pquis/Management-of-Abemaciclib-Verzenio-Associated-Diarrhea_PQI_NCODA.pdf
17. Summary of product characteristics [Internet]. Accessed January 1, 2021. https://www.ema.europa.eu/en/documents/product-information/verzenios-epar-product-information_en.pdf
18. Thibault S, Hu W, Hirakawa B, et al. Intestinal toxicity in rats following administration of CDK4/6 inhibitors is independent of primary pharmacology. *Mol Cancer Ther*. 2019;18(2):257-266. https://doi.org/10.1158/1535-7163.MCT-18-0734
19. Fuentes-Antrás J, de Luna A, López de Sá A, et al. Safety and efficacy of cyclindependent kinase inhibitor rechallenge following ribociclib-induced limiting hypertransaminasemia. *Breast*. 2020;54:160-163. https://doi.org/10.1016/j.breast.2020.10.007
20. Zurcher JP, Goujon M, Cottu PH, et al. Feasibility of treatment with another CDK4/6 inhibitor after severe ribociclib liver toxicity. *J Clin Oncol*. 2023;41(16_suppl):e13067-e13067. https://doi.org/10.1200/jco.2023.41.16_suppl.e13067
21. Benvenuti C, Viansone A, Jacobs F, et al. Switching cyclin-dependent kinase inhibitors (CDK4/6i) in patients with hormone receptor-positive (HR+)/human epidermal growth factor-negative (HER2-) advanced breast cancer (ABC) who experienced unacceptable toxicity. Accepted for poster presentation for ESMO BREAST congress; May 2024; Berlin.
22. Hurvitz SA, Martin M, Press MF, et al. Potent cell-cycle inhibition and upregulation of immune response with abemaciclib and anastrozole in neoMONARCH, phase II neoadjuvant study in HR+/HER2- breast cancer. *Clin Cancer Res*. 2020;26(3):566-580. https://doi.org/10.1158/1078-0432.CCR-19-1425
23. Dickler MN, Tolaney SM, Rugo HS, et al. MONARCH 1, a phase II study of abemaciclib, a CDK4 and CDK6 inhibitor, as a single agent, in patients with refractory HR+/HER2- metastatic breast cancer. *Clin Cancer Res*. 2017;23(17):5218-5224. https://doi.org/10.1158/1078-0432.CCR-17-0754
24. Basch E, Jia X, Heller G, et al. Adverse symptom event reporting by patients vs clinicians: relationships with clinical outcomes. *J Natl Cancer Inst*. 2009;101(23):1624-1632. https://doi.org/10.1093/jnci/djp386
25. Atkinson TM, Dueck AC, Satele DV, et al. Clinician vs patient reporting of baseline and postbaseline symptoms for adverse event assessment in cancer clinical trials. *JAMA Oncol*. 2020;6(3):437-439. https://doi.org/10.1001/jamaoncol.2019.5566
26. Masuda H, Tanabe Y, Sakai H, et al. Efficacy of probiotics and trimebutine maleate for abemaciclib-induced diarrhea: a randomized, open-label phase II trial (MERMAID, WJOG11318B). *Breast*. 2023;71:22-28. https://doi.org/10.1016/j.breast.2023.07.003