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Safety of Abemaciclib in Indian Patients with Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Locally Advanced and/or Metastatic Breast Cancer: A Multicenter, Nonrandomized, Open-Label, Single-Arm, Phase 4 Study

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Abstract

Background Global phase III trials demonstrated efficacy of abemaciclib in patients with HR +/HER2– metastatic breast cancer (BC) as a first-line therapy in combination with a nonsteroidal aromatase inhibitor (MONARCH-3) or with fulvestrant following progression after endocrine therapy (ET) (MONARCH-2). However, there is limited data on safety and tolerability of abemaciclib plus ET in the metastatic BC setting among Indian patients, which the present study aims to address.

Materials and Methods An open-label, single-arm, phase IV study was conducted across 16 centers in India to assess the safety and tolerability of abemaciclib in patients with HR +/HER2– locally advanced or metastatic BC. Patients were assigned to either cohort A, ET-naive patients (abemaciclib + anastrozole/letrozole) or cohort B, patients progressing after previous ET (abemaciclib + fulvestrant), targeting the same patient

Keywords
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- abemaciclib
- advanced breast cancer
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population as the global phase III MONARCH-3 and MONARCH-2 trials, respectively. Primary endpoints were all-cause adverse events (AEs) including serious AEs (SAEs).

Statistical Analysis The statistical analysis was conducted using SAS Version 9.4.

Results Two hundred patients were enrolled, with a mean age of 54 years, most (77.0%) were aged $\leq$ 65 years. The median duration of exposure was similar in both cohorts (cohort A vs. B: 24.3 vs. 24.4 weeks). Overall, 75.5 % of patients reported all-cause AEs, of which 38.5% of the patients reported AEs Common Terminology Criteria for Adverse Events grade 3 and above. The most common grade 3 and above all-cause AEs for abemaciclib were neutropenia (19.0%), followed by anemia (14.0%) and diarrhea (5.5%). Fourteen (7.0%) patients encountered SAEs, including infections (2.0%) and gastrointestinal disorders (1.5%). Most of the patients continued their treatments with appropriate dose reductions (25.5%) and dose omissions (40.5%), and only 2.5% of patients discontinued study treatment due to treatment-related AEs.

Conclusion Abemaciclib in combination with ET was found to have an acceptable tolerability in Indian patients with HR +/HER2– advanced and metastatic BC, consistent with the established safety data as reported in the pivotal global studies. No new clinical safety concerns were identified, with most of the reported AEs and SAEs managed by dose adjustments.

Introduction

Breast cancer (BC) is the leading form of cancer among women and the primary cause of cancer-related mortality, with approximately 2.3 million new cases and over 666,103 deaths reported in 2022 worldwide.[1] In India, there were reportedly 192,020 new cases of BC, and a cumulative 98,337 deaths throughout that year.[2] This indicates a substantial increase in incidence and mortality from the 2020 estimates of 178,361 new cases and 90,408 cumulative deaths.[3] New BC cases constituted more than one-fourth of all new female cancer cases in India in 2022.[4] Among new cases, it is estimated that about 20 to 30% of women first diagnosed with early-stage BC progress to advanced or metastatic disease,[5] which typically has a low median overall survival of 2 to 3 years and a 5-year survival rate of 25%.[6]

Treatment selection for advanced BC depends on hormone receptor (HR) status and the level of HER2 expression in the tumor tissue.[6] Previously, endocrine therapy (ET) with nonsteroidal aromatase inhibitors (NSAIs) or fulvestrant was the preferred initial treatment for HR +/HER2– advanced BC.[6] However, this treatment approach often resulted in a condition wherein tumors became resistant to standard ET.[7] This was an unmet medical need and required new drugs to evaluate for preventing or delaying the development of endocrine resistance. Since the approval of cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) therapy, ET in combination with CDK4/6i (palbociclib, ribociclib, and abemaciclib) is the standard of care for HR +/HER2– metastatic BC,[8] and multiple guidelines, such as those from the European Society for Medical Oncology,[9] the National Comprehensive Cancer Network,[10] and the American Society of Clinical Oncology,[11] recommend the use of ET plus CDK4/6i for the treatment of certain HR +/HER2– metastatic BC patients.

Abemaciclib is a selective small-molecule inhibitor that can be administered orally as part of a continuous schedule, unlike other CDK4/6 inhibitors that require 1 week off the drug at the end of each cycle of treatment.[12] Abemaciclib was the first CDK4/6 inhibitor to be approved for use in combination with fulvestrant in women with HR +/HER2– advanced or metastatic BC with disease progression following ET.[13] In enzymatic assays, abemaciclib has demonstrated 14 times more potency against CDK4/cyclin D1 than CDK6/cyclin D3.[14–16] Further, preclinical studies have shown that abemaciclib promotes sustained growth arrest during continued inhibition, causing apoptosis or cellular senescence and G1 arrest upon short-term exposure.[17,18] Abemaciclib in combination with ET (either NSAI or fulvestrant) has demonstrated improved progression-free survival (PFS) and overall survival over ET alone in treating patients with HR +/HER2– advanced BC.[19,20]

The MONARCH 2 and MONARCH 3 studies are pivotal global phase 3 trials that have consistently demonstrated the substantial efficacy and tolerable safety of abemaciclib in combination with fulvestrant and anastrozole or letrozole in the context of HR +/HER2– advanced BC, respectively.[16,19–21] The MONARCH plus phase 3 study included patients with HR +/HER2– advanced or metastatic BC from China, Brazil, South Africa, and India and reported that the efficacy and safety of abemaciclib plus ET were consistent with the results of MONARCH 2 and 3.[22] The number of patients with BC from India who participated in the aforementioned research, however, was limited, which meant that the safety profile of abemaciclib in this population was not well described.[23] Furthermore, there are limited studies on the impact of ethnicity on efficacy and toxicity of abemaciclib/ET combination therapies.[24,25] To address lack of published safety data in Indian patients and as part of a postapproval commitment,

a single-arm, open-label phase 4 study was designed to prospectively assess the safety and tolerability of abemaciclib in combination with ET in Indian patients with HR+/HER2– locally advanced or metastatic BC.

Methods

Study Setting

The present study was a nonrandomized, open-label, single-arm, phase IV cohort study conducted across 16 centers in India from February 2021 to April 2023. This study was designed to assess the safety and tolerability of abemaciclib when used in combination with an NSAI (anastrozole or letrozole) based on investigator's choice, or fulvestrant, in patients with HR+/HER2– locally advanced or metastatic BC. The study's protocol (I3Y-IN-JPEC) received approval from the ethics committees of all the participating centers. It adhered to ethical principles from international guidelines such as the Declaration of Helsinki, the Council for International Organizations of Medical Sciences, and the International Conference on Harmonisation's Good Clinical Practice guidelines, in addition to relevant laws and regulations (Clinicaltrials.gov - NCT04707196; Clinical Trials Registry - India [CTRI] - CTRI/2020/12/030021). All patients provided written informed consent before enrollment.

Patients

Female patients aged 18 years or older with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 diagnosed with either HR+/HER2– locoregionally recurrent BC or HR+/HER2– metastatic BC and capable of swallowing oral formulations of pharmaceutical products were included in this study. The study excluded patients with the following conditions: visceral crisis, lymphangitic spread, leptomeningeal carcinomatosis, history of metastasis in the brain, recent live vaccinations (except seasonal nonlive flu shots), history of presyncope/syncope, inflammatory BC or history of other cancers (except nonmelanoma skin cancer or carcinoma in situ of the cervix) not in remission for at least 3 years, history of stem cell transplant, or active infections. Patients previously treated with chemotherapy (excluding neoadjuvant or adjuvant chemotherapy), fulvestrant, everolimus, or any CDK4/6 inhibitor were also excluded.

Study Intervention, Dosage, and Treatment Duration

Cohort A included ET-naive patients scheduled for initial ET for advanced/metastatic BC, while cohort B comprised ET pretreated patients for advanced/metastatic BC or those who had a relapse during or within a year after adjuvant ET. Patients in cohort A received 150 mg of abemaciclib twice daily in combination with investigator's choice of anastrozole 1 mg or letrozole 2.5 mg once daily for 28 days as oral administration. Patients in cohort B received abemaciclib at the same dosage and schedule as cohort A, in combination with an intramuscular injection of the standard dosage of fulvestrant (500 mg over a 28-day cycle based on the dosing schedule mentioned in the local prescribing information). The study was designed to enroll approximately 200 patients in India, targeting the same patient population as the global phase 3 MONARCH 3 and MONARCH 2 trials. The study treatment was continued for a total duration of six cycles or less in case of radiographic or clinical progression as per investigator's judgment or another discontinuation criterion being met. Participants who completed the study after six cycles of treatment continued to receive abemaciclib (through a patient support program) as per investigator's discretion. A short-term (30 days +7) posttreatment follow-up was conducted when participant and investigator agreed that the participant would no longer continue study treatment, for participants who discontinued study treatment prior to completion of six cycles, or for participants who completed six cycles but did not continue to receive abemaciclib.

Primary and Secondary Endpoints

The primary endpoints were all-cause adverse events (AEs), serious AEs (SAEs), and AEs of special interest, as classified by the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. The secondary endpoint was the incidence of abemaciclib discontinuation due to an AE.

Study Assessments and Procedures

All patients who received at least one dose of the study treatment were evaluated for safety and tolerability. The safety analysis included summaries of AEs, SAEs, reasons for discontinuation due to AEs, dose adjustments, laboratory values, vital signs, and electrocardiogram readings. AEs were recorded at each visit using NCI CTCAE v5.0 criteria. Safety laboratory assessments were conducted on day 1 and day 14 for the first two cycles, and on day 1 and day 28 for the following four cycles. Information on drug exposure, patient completion rates, and dose intensity was also collected. Deaths not related to HR+/HER2– locally advanced or metastatic BC were reported with their causes. A detailed narrative was provided for deaths related to an AE or any cause during or within 30 days of treatment. Tumor assessments were conducted at baseline (within 28 days before the first dose) and subsequently every 12 weeks following local standard practices. Unscheduled tumor assessments were performed during the study when clinically necessary, but no formal efficacy evaluations were carried out.

Dose Modifications

Dose adjustments (dose omission and dose reductions) were performed based on clinical assessments of hematologic and nonhematologic toxicities, as per the investigator's judgment. Abemaciclib dose omission may extend up to 28 days to allow for recovery from treatment-emergent toxicities. Patients not recovering may be permanently discontinued from abemaciclib treatment.

Statistical Analysis

The statistical analysis was conducted using SAS Version 9.4 (SAS Institute, North Carolina, United States). Safety analyses were conducted on the safety population, which included all patients who had received at least one dose of the study treatment. While categorical variables were characterized by

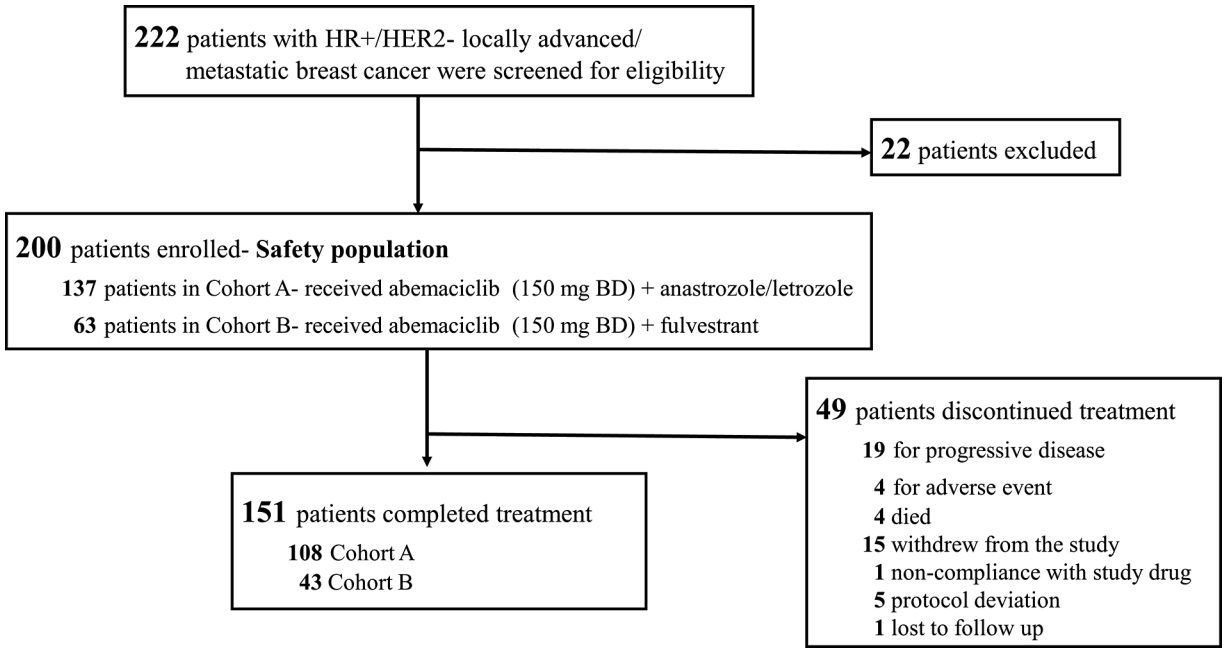

Fig. 1 Study design and patient disposition. HR +/HER2–: hormone receptor-positive/human epidermal growth factor receptor 2 negative; BD, twice daily.

their frequencies and occurrence percentages, continuous variables were presented using means, medians, standard deviations, and the range of minimum to maximum values.

Results

Study Participants

Of the 222 patients assessed for eligibility, 200 were enrolled (cohort A: 137; cohort B: 63) and received at least one dose of the study medication. As of the data cutoff date, a total of 151 patients (75.5%) completed the study (►**Fig. 1**).

Baseline Demographics and Disease Characteristics

The study involved female patients with an average age of 54 years (standard deviation: 12.05; range: 26–81 years), most (77.0%) of whom were aged 65 or younger. About one-fourth (27.0%) of the patients had visceral metastases, while 6.0% had bone-only metastases. Most (73.0%) patients had an ECOG performance status of 1, and almost all (99.0%) were in stage IV of the disease. For prior therapies, almost half of the patients (48.5%) underwent surgery, and a similar proportion (49.5%) received systemic therapy, of whom 43.5% received adjuvant therapy and 10.5% received neoadjuvant therapy (►**Table 1**). Most (89.5%) patients were administered one or more concomitant medications. The most frequently used therapies were zoledronic acid (40%), goserelin (24%), vitamin and mineral supplementation (cholecalciferol, 24%; calcium, 20%), folic acid (14%), paracetamol (14%), filgrastim (13%), and pantoprazole (12%).

Exposure and Treatment Compliance

A total of 75.5% of the patients completed six cycles of therapy. The median duration of exposure was 24.3 weeks for cohort A (ranging from 0.9 to 33.9 weeks) and 24.4 weeks for cohort B (ranging from 0.7 to 31.0 weeks) (►**Supplementary Table S1**, available in online version only). Both cohort A and cohort B exhibited high treatment compliance, with median rates of 93.9 and 92.9%, respectively (►**Supplementary Table S2**, available in online version only).

All-Cause and Treatment-Related AEs

Approximately 75.5% of the patients experienced at least one AE regardless of causality, with no significant differences noted between treatment cohorts. About 40.5% of the overall patients experienced grade 3 or above AEs (all-cause) of higher severity. The most common grade 3 all-cause AEs were neutropenia and anemia (15.3% each) followed by leukopenia (5.8%) for cohort A, and neutropenia (22.2%) followed by anemia (9.5%) and diarrhea (6.3%) for cohort B (►**Table 2**). The incidence of treatment-related AEs was comparable to that of all-cause AEs by maximum CTCAE, with no new safety concerns identified.

All-Cause AEs Leading to Dose Adjustments

The dose adjustments resulting from AEs included dose omission, reduction, and treatment discontinuation. In cohort A 58 patients (42.3%) and in cohort B 28 patients (44.4%) had abemaciclib dose omissions because of AEs. Additionally, five patients (3.6%) within cohort A had anastrozole or letrozole dose omissions and three patients (4.8%) in cohort B had fulvestrant dose omission for the same reasons. The most common AEs (all-cause) leading to dose omissions were neutropenia (cohort A: 27.8%; cohort B: 37.0%), anemia (cohort A: 25.9%; cohort B: 14.8%), and diarrhea (cohort A: 24.1%; cohort B: 29.6%) (►**Table 3**).

The proportion of patients requiring dose reductions was similar across treatment cohorts (cohort A: 24.8%, cohort B: 28.6%). Diarrhea (cohort A: 33.3%; cohort B: 27.8%) and neutropenia (cohort A: 24.2%; cohort B: 38.9%) were the most common AEs (all-cause), leading to a dose reduction of

Table 1 Demographics and baseline characteristics

Category	Cohort A ($N=137$) ($n=\%$)	Cohort B ($N=63$) n (%)	Overall ($N=200$) n (%)
Age (y)			
n	137	63	200
Mean (SD)	55.6 (11.66)	51.8 (12.54)	54.4 (12.05)
Median	57.0	50.0	55.0
Min, Max	26, 81	32, 79	26, 81
Age categories, *n* (%)			
<65 y	105 (76.6)	49 (77.8)	154 (77.0)
≥ 65 y	32 (23.4)	14 (22.2)	46 (23.0)
Pathological diagnosis basis at initial diagnosis (*n* [%])[a]			
No. of patients	66 (48.2)	28 (44.4)	94 (47.0)
Cytological	6 (4.4)	6 (9.5)	12 (6.0)
Histopathological	60 (43.8)	22 (34.9)	82 (41.0)
Nature of disease			
No. of patients	137 (100.0)	63 (100.0)	200 (100.0)
Visceral[b]	42 (30.7)	12 (19.0)	54 (27.0)
Bone only	17 (12.4)	8 (12.7)	25 (12.5)
Other	78 (56.9)	43 (68.3)	121 (60.5)
Baseline ECOG performance status (*n* [%])			
No. of patients	137 (100.0)	63 (100.0)	200 (100.0)
0	46 (33.6)	8 (12.7)	54 (27.0)
1	91 (66.4)	55 (87.3)	146 (73.0)
Disease stage at study entry (*n* [%])			
No. of patients	137 (100.0)	63 (100.0)	200 (100.0)
Stage III	2 (1.5)	0 (0.0)	2 (1.0)
Stage IV	135 (98.5)	63 (100.0)	198 (99.0)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; HER, human epidermal growth factor receptor; *N*, number of participants in population; *n*, number of participants within category (numerator for percent calculations); PR, progesterone receptor; SD, standard deviation.

Note: Cohort A: abemaciclib + anastrozole or letrozole; cohort B: abemaciclib + fulvestrant.

[a]Pathological diagnosis information that was not collected in the electronic case report form is reported as missing. Inclusion criteria for ER, PR, and HER based on pathological diagnosis were confirmed by source data verification.

[b]Visceral disease is defined as soft tissue lesions involving the liver, lungs, adrenal glands, peritoneum, pleura, brain, and dura.

abemaciclib. However, dose reductions due to neutropenia were more frequent in cohort B (38.9%) compared with cohort A (24.2%) (►Table 3).

Overall, eight patients (4.0%) discontinued study treatment due to AEs, of whom five (2.5%) discontinued due to AEs associated with the study drug. In cohort A, AEs causing treatment discontinuation were vomiting ($n=1$), death ($n=1$), cardiorespiratory arrest ($n=1$), decreased white blood cell counts ($n=1$), and pneumonitis ($n=1$). In cohort B, AEs leading to treatment discontinuation were anemia with diarrhea ($n=1$), asthenia ($n=1$), and neutropenic sepsis ($n=1$) (►Table 3).

Serious Adverse Events

Among overall study population, 14 (7.0%) patients encountered SAEs, 7 (3.5%) (cohort A: 4 [2.9%]; cohort B: 3 [4.8%] patients) were deemed to have SAEs that were possibly related to the study treatment. Major SAEs were related to infections (overall: 2.0%; cohort A: 0.7%; cohort B: 4.8%) and gastrointestinal disorders (overall: 1.5%; cohort A: 2.2%; cohort B: 0.0%) (►Table 4). During the study, four patients died, and two of these deaths were adjudged to be related to the drug. Within cohort A, one death occurred from pneumonitis, while in cohort B, one death was caused by neutropenic sepsis.

The overview of all AEs experienced by the safety population has been depicted in ►Table 5.

Discussion

This study is the first phase 4 clinical trial evaluating the safety of abemaciclib in women with HR+/HER2– locally

Table 2 All-cause and treatment-related AEs by maximum CTCAE grade occurring in at least 10% of patients

	Cohort A ($N=137$) *n* (%)			Cohort B ($N=63$) *n* (%)		
Preferred term	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4
All-cause AEs						
Patients with any AE, *n* (%)	107 (78.1)	47 (34.3)	3 (2.2)	44 (69.8)	24 (38.1)	3 (4.8)
Diarrhea	42 (30.7)	7 (5.1)	0 (0.0)	18 (28.6)	4 (6.3)	0 (0.0)
Neutropenia[a]	40 (29.2)	21 (15.3)	1 (0.7)	20 (31.7)	14 (22.2)	2 (3.2)
Anemia[b]	33 (24.1)	21 (15.3)	1 (0.7)	14 (22.2)	6 (9.5)	0 (0.0)
Leukopenia[c]	25 (18.2)	8 (5.8)	0 (0.0)	13 (20.6)	2 (3.2)	0 (0.0)
Vomiting	18 (13.1)	1 (0.7)	0 (0.0)	13 (20.6)	2 (3.2)	0 (0.0)
Fatigue[d]	14 (10.2)	3 (2.2)	0 (0.0)	15 (23.8)	2 (3.2)	0 (0.0)
Nausea	14 (10.2)	0 (0.0)	0 (0.0)	10 (15.9)	0 (0.0)	0 (0.0)
Cough	0 (0.0)	0 (0.0)	0 (0.0)	8 (12.7)	1 (1.6)	0 (0.0)
Treatment-related AEs						
Patients with any drug-related AE, *n* (%)	89 (65.0)	42 (30.7)	3 (2.2)	41 (65.1)	22 (34.9)	3 (4.8)
Diarrhea	40 (29.2)	7 (5.1)	0 (0.0)	18 (28.6)	4 (6.3)	0 (0.0)
Neutropenia[a]	36 (26.3)	19 (13.9)	1 (0.7)	19 (30.2)	14 (22.2)	2 (3.2)
Anemia	29 (21.2)	19 (13.9)	1 (0.7)	13 (20.6)	6 (9.5)	0 (0.0)
Leukopenia	20 (14.6)	8 (5.8)	0 (0.0)	12 (19.0)	2 (3.2)	0 (0.0)
Nausea	13 (9.5)	0 (0.0)	0 (0.0)	8 (12.7)	0 (0.0)	0 (0.0)
Vomiting	13 (9.5)	0 (0.0)	0 (0.0)	12 (19.0)	2 (3.2)	0 (0.0)
Fatigue[d]	12 (8.8)	3 (2.2)	0 (0.0)	13 (20.6)	2 (3.2)	0 (0.0)
Abdominal pain[e]	10 (7.3)	0 (0.0)	0 (0.0)	8 (12.7)	0 (0.0)	0 (0.0)

Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; *n*, participants count in specified category; *N*, number of participants in relevant treatment arm with safety population.
Note: CTCAE Version 5.0. Cohort A: abemaciclib + anastrozole or letrozole, cohort B: abemaciclib + fulvestrant.
[a]Neutropenia, as a consolidated term, was defined as neutropenia and decreased neutrophil counts.
[b]Anemia, as a consolidated term, was defined as anemia, decreased hematocrit, decreased hemoglobin, and decreased red blood cell counts.
[c]Leukopenia, as a consolidated term, was defined as leukopenia and decreased white blood cell counts.
[d]Fatigue, as a consolidated term, was defined as asthenia and fatigue.
[e]Abdominal pain, as a consolidated term, was defined as abdominal discomfort, abdominal pain, lower abdominal pain, upper abdominal pain upper, and gastrointestinal pain.

advanced or metastatic BC in India. In the present study, patients were treated with abemaciclib plus NSAI (anastrozole or letrozole) in cohort A and abemaciclib plus fulvestrant in cohort B, following the design of two pivotal global trials, viz., MONARCH 3 (abemaciclib plus anastrozole or letrozole) and MONARCH 2 (abemaciclib plus fulvestrant), respectively. The MONARCH trials demonstrated significant improvements in PFS and the objective response rate, besides an acceptable safety profile, in patients with HR+/HER2– advanced and metastatic BC.[16,21,26]

In the current study, adult female patients across various age groups were included. In the overall population, 75.5% of patients reported all-cause AEs, with 38.5% of the patients reporting CTCAE grade 3 and above AEs. The most common grade 3 and above treatment-related AEs for abemaciclib were neutropenia (18.0%), followed by anemia (13.0%) and diarrhea (5.5%). Nevertheless, most of the patients continued their treatments with appropriate dose reductions (25.5%) and dose omissions (40.5%), with only 2.5% of patients discontinuing the study treatment because of treatment-related AEs. These results suggest that abemaciclib was overall tolerable to the majority of patients, and dose adjustments played a key role in keeping the patients on treatment.

In the overall population, neutropenia by CTCAE grade 3 and above was reported in 19% of the patients. While in our study, the incidence of grade 3 or higher neutropenia was 16.0% in cohort A, it was 23.8% in the MONARCH 3 trial. In cohort B, grade 3 or higher neutropenia was 25.4% in our study, whereas it was 26.5% in the MONARCH 2 trial.[27] In the present study, approximately 8% of patients had dose reductions, while 10.0% of patients in MONARCH 2 and 12.8% in MONARCH 3 had dose reductions due to neutropenia. Similarly, in our study approximately 13% of patients required dose omission, whereas 16.3% of patients in MONARCH 2 and 17.4% of patients in MONARCH 3 trial had dose omission due to neutropenia.[27] In the current study, no patients discontinued treatment due to neutropenia.

Table 3 All-cause AEs leading to dose adjustments in at least 10% of patients

	Cohort A ($N = 137$) *n* (%)		Cohort B ($N = 63$) *n* (%)	
	Abemaciclib	Anastrozole or letrozole	Abemaciclib	Fulvestrant
All-cause AEs leading to dose omissions				
Number of subjects with dose omission	58 (42.3)	5 (3.6)	28 (44.4)	3 (4.8)
Reasons for dose omission				
Adverse event	54 (93.1)	5 (100)	27 (96.4)	3 (100)
Anemia	14 (25.9)	0 (0.0)	4 (14.8)	0 (0.0)
Diarrhea	13 (24.1)	1 (20.0)	8 (29.6)	0 (0.0)
Neutropenia[a]	15 (27.8)	0 (0.0)	10 (37.0)	0 (0.0)
Blood creatinine increased	8 (14.8)	0 (0.0)	0 (0.0)	0 (0.0)
Leukopenia	7 (13.0)	0 (0.0)	1 (3.7)	0 (0.0)
COVID-19	3 (5.6)	2 (40.0)	2 (7.4)	1 (33.3)
Aspartate aminotransferase increased	1 (1.9)	1 (20.0)	0 (0.0)	0 (0.0)
Gastroenteritis	1 (1.9)	1 (20.0)	0 (0.0)	0 (0.0)
Pulmonary hypertension	1 (1.9)	1 (20.0)	0 (0.0)	0 (0.0)
COVID-19 pneumonia	0 (0.0)	0 (0.0)	1 (3.7)	1 (33.3)
Urinary tract infection pseudomonal	0 (0.0)	0 (0.0)	1 (3.7)	1 (33.3)
Fatigue[b]	0 (0.0)	0 (0.0)	3 (11.1)	0 (0.0)
All-cause AEs leading to dose reduction				
Number of subjects with dose reduction	34 (24.8)	–	18 (28.6)	–
Reasons for dose reduction				
Adverse event	33 (97.1)	–	18 (100)	–
Diarrhea	11 (33.3)	–	5 (27.8)	–
Neutropenia[a]	8 (24.2)	–	7 (38.9)	–
Blood creatinine increased	5 (15.2)	–	0 (0.0)	–
Leukopenia	5 (15.2)	–	1 (5.6)	–
Anemia	3 (9.1)	–	2 (11.1)	–
Thrombocytopenia	0 (0.0)	–	2 (11.1)	–

Abbreviations: AE, adverse event; COVID-19, coronavirus disease 2019; MedDRA, Medical Dictionary for Regulatory Activities; *N*, number of participants in relevant treatment arm with safety population; *n*, number of participants in specified category.
Note: MedDRA Version 25.0. Cohort A: abemaciclib + anastrozole or letrozole, cohort B: abemaciclib + fulvestrant.
No AEs leading to dose adjustment in at least 10% of patients were related to anastrozole, letrozole, or fulvestrant use.
Percentages of adverse events are calculated based on the number of subjects with reasons for dose omission due to adverse events.
[a]Neutropenia, as a consolidated term, was defined as neutropenia and decreased neutrophil counts.
[b]Fatigue, as a consolidated term, was defined as asthenia and fatigue.

The study revealed that 5.5% of the overall population experienced diarrhea classified as CTCAE grade 3 or higher. In cohort A, 5.1% of patients experienced CTCAE grade 3 diarrhea due to abemaciclib, which is lower than the 9.5% reported in the MONARCH 3 trial. Similarly, 6.3% of patients in cohort B had grade 3 diarrhea, compared with 13.4% in the MONARCH 2 trial.[16,26] This decrease in the rates and severity of diarrhea observed in our study versus the other MONARCH studies may be attributed to differences in the regional and ethnic backgrounds of patients, affecting their perception, acceptance, and tolerance of the condition.[25,27] Overall, diarrhea was manageable with antidiarrheal therapy and dose adjustments. In our study, approximately 8% of patients had dose reduction due to diarrhea, while 18.8% of patients in the MONARCH 2 and 13.8% of patients in MONARCH 3 trial had dose reduction due to diarrhea. Similarly, in our study approximately 11% of patients had dose omission, whereas 18.8% of patients in the MONARCH 2 and 15.3% of patients in MONARCH 3 trial had dose omission due to diarrhea.[27] Only one patient discontinued treatment due to diarrhea in the present study. The enhanced real-world experience being gained by oncologists with abemaciclib has led to better counseling and management of diarrhea. A recently published consensus statement on CDK4/6i usage

Table 4 Summary of serious adverse events

Primary SOC preferred term	Cohort A ($N = 137$) *n* (%)	Cohort B ($N = 63$) *n* (%)	Overall ($N = 200$) *n* (%)
Subject with at least one SAE	9 (6.6)	5 (7.9)	14 (7.0)
Infections	1 (0.7)	3 (4.8)	4 (2.0)
COVID-19 pneumonia	0 (0.0)	1 (1.6)	1 (0.5)
Gastroenteritis	1 (0.7)	0 (0.0)	1 (0.5)
Neutropenic sepsis	0 (0.0)	1 (1.6)	1 (0.5)
Urinary tract infection pseudomonal	0 (0.0)	1 (1.6)	1 (0.5)
Gastrointestinal disorders	3 (2.2)	0 (0.0)	3 (1.5)
Diarrhea	1 (0.7)	0 (0.0)	1 (0.5)
Gastritis	1 (0.7)	0 (0.0)	1 (0.5)
Hemorrhoidal hemorrhage	1 (0.7)	0 (0.0)	1 (0.5)
Vomiting	1 (0.7)	0 (0.0)	1 (0.5)
General disorders and administration-site conditions	2 (1.5)	1 (1.6)	3 (1.5)
Death	1 (0.7)	0 (0.0)	1 (0.5)
Multiple organ dysfunction syndrome	0 (0.0)	1 (1.6)	1 (0.5)
Pyrexia	1 (0.7)	0 (0.0)	1 (0.5)
Blood and lymphatic system disorders	1 (0.7)	1 (1.6)	2 (1.0)
Pancytopenia	1 (0.7)	0 (0.0)	1 (0.5)
Thrombocytopenia	0 (0.0)	1 (1.6)	1 (0.5)
Cardiac disorders	1 (0.7)	1 (1.6)	2 (1.0)
Cardiac failure congestive	0 (0.0)	1 (1.6)	1 (0.5)
Cardiorespiratory arrest	1 (0.7)	0 (0.0)	1 (0.5)
Respiratory, thoracic, and mediastinal disorders	2 (1.5)	0 (0.0)	2 (1.0)
Pneumonitis	1 (0.7)	0 (0.0)	1 (0.5)
Pulmonary embolism	1 (0.7)	0 (0.0)	1 (0.5)
Pulmonary hypertension	1 (0.7)	0 (0.0)	1 (0.5)
Musculoskeletal and connective tissue disorders	0 (0.0)	1 (1.6)	1 (0.5)
Pathological fracture	0 (0.0)	1 (1.6)	1 (0.5)

Abbreviations: COVID-19, coronavirus disease 2019; MedDRA, Medical Dictionary for Regulatory Activities; *N*, number of participants in relevant treatment arm with safety population; *n*, number of participants in specified category; SOC, system organ class; SAE, serious adverse event.
Note: MedDRA Version 25.0. Cohort A: abemaciclib + anastrozole or letrozole, cohort B: abemaciclib + fulvestrant.
[a]Gastroenteritis, as a consolidated term, was defined as gastroenteritis, gastric infection, gastroenteritis viral, and gastrointestinal infection.
[b]Thrombocytopenia, as a consolidated term, was defined as thrombocytopenia and decreased platelet counts.

has attributed the lower incidence of abemaciclib-associated diarrhea to high consumption of curd in the Indian population.[28]

In this study, the incidence of anemia by CTCAE grade 3 and above was reported in 14.0% of the patients in the overall population. Furthermore, anemia by CTCAE grade 3 and higher was observed among 16.0% of patients in cohort A, compared with 5.8% in the MONARCH 3 trial, whereas 9.5% of patients in cohort B reported AEs compared with 7.2% in the MONARCH 2 trial. The condition was managed by dose adjustments for approximately 9% of the patients; however, one patient discontinued the study due to anemia. Higher rates of severe anemia are typically related to poor nutrition and postmenopausal status, as anemia is prevalent among approximately 85% of postmenopausal women in India.[29] However, our study revealed that the incidence of both anemia and neutropenia were predictable and similar to the MONARCH trials and easily managed by dose adjustments. Although dose reductions following AEs are required, they do not lead to a decrease in the efficacy of abemaciclib.[27]

The present study reported a lower incidence of SAEs compared with the MONARCH studies.[16,26] In our study, 7.0% of patients reported SAEs compared with 22.4% in the abemaciclib arm of MONARCH 2 trial and 27.5% in the MONARCH 3 trial.[16,26] Additionally, 3.5% patients in our study had SAEs related to the study treatment compared with 8.8% the MONARCH 2 trial.[16]

Table 5 Overview of adverse events

	Cohort A (*N* = 137) *n* (%)	Cohort B (*N* = 63) *n* (%)	Overall (*N* = 200) *n* (%)
Patients with ≥ 1 AE regardless of causality	107 (78.1)	44 (69.8)	151 (75.5)
related to study treatment	89 (65.0)	41 (65.1)	130 (65.0)
Patients with ≥ 1 CTCAE ≥ grade 3 AE regardless of causality	53 (38.7)	28 (44.4)	81 (40.5)
related to study treatment	46 (33.6)	26 (41.2)	72 (36)
Patients with ≥ 1 SAE regardless of causality	9 (6.6)	5 (7.9)	14 (7.0)
related to study treatment	4 (2.9)	3 (4.8)	7 (3.5)
Patients who discontinued study treatment due to an AE regardless of causality	5 (3.6)	3 (4.8)	8 (4.0)
related to study treatment	2 (1.5)	3 (4.8)	5 (2.5)
Patients who died due to an AE on study treatment regardless of causality	3 (2.2)	1 (1.6)	4 (2.0)
related to study treatment	1 (0.7)	1 (1.6)	2 (1.0)

Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; *N*, number of participants in relevant treatment arm with safety population; *n*, number of participants in specified category; SAE, serious adverse event.
Note: Cohort A: abemaciclib + anastrozole or letrozole; cohort B: abemaciclib + fulvestrant.
Patients may be counted in more than one category.

This study had a few limitations such as the study was conducted at 16 hospitals across India, hence generalization of the finding for the entire population in India should be done with caution. Furthermore, differences in baseline demographic and clinical characteristics among the subgroups (cohort A and cohort B) could potentially affect the perception of safety profile of the treatment. Another possible limitation of the study was that cohort B had a smaller sample size compared with cohort A; however, the safety results reported were robust when compared and interpreted against the large global MONARCH 2 and 3 trials. Additionally, the study had a relatively short period of data collection (only 6 months), which provides good information about the short-term toxicities but does not capture toxicities associated with long-term abemaciclib exposure.

Conclusion

This is the first postmarketing phase IV clinical study report from India on the safety and use of abemaciclib in combination with an aromatase inhibitor or fulvestrant for locally advanced and metastatic BC. The findings reveal that the safety profile of abemaciclib in combination with ET in the Indian population was consistent with the established safety data of abemaciclib plus ET in adult patients with HR+/HER2– advanced and metastatic BC as reported in the pivotal global studies, that is, MONARCH 2 and 3. The AEs reported were as expected and manageable through dose adjustments and supportive care. Of note, no new clinically significant safety concerns were identified in this Indian study population.

Authors' Contributions

All authors contributed significantly to the study. D.C.D., T.M., R.N., S.C.T., R.T., S.P., A.T. M., M.J., D.M., P.N.M. and S.G. were involved in the acquisition and interpretation of data, critical revision of the manuscript, and approval of the final version of the manuscript. S.G. also contributed to the acquisition and interpretation of data, critical revision of the manuscript, and approval of the final version. K.N.S. played a key role in interpreting the results, preparing the manuscript draft, and approving the final version. A.P. and R.A. contributed to the conception and design of the study, interpretation of the data, critical revision of the manuscript, and approval of the final version. All authors have approved the final manuscript.

Ethical Approval and Statement of Conforming to the Declaration of Helsinki

The study's protocol (I3Y-IN-JPEC) received approval from the ethics committees of all the participating centers. It adhered to ethical principles from international guidelines such as the Declaration of Helsinki, the Council for International Organizations of Medical Sciences (CIOMS), and the International Conference on Harmonisation's (ICH) Good Clinical Practice (GCP) guidelines, in addition to relevant laws and regulations (Clinicaltrials.gov - NCT04707196; Clinical Trials Registry - India (CTRI) - CTRI/2020/12/030021). All patients provided written informed consent before enrollment.

Trial Registration Numbers

Clinicaltrials.gov - NCT04707196 and Clinical Trials Registry - India (CTRI) - CTRI/2020/12/030021.

Conflict of Interest

K.N.S., A.P., and R.A. are employees and shareholders of Eli Lilly and Company. None declared by the other authors.

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