



Safety and Efficacy of Ribociclib in Combination with Letrozole in Patients with HR+, HER2– Advanced Breast Cancer: Results from the Italian Subpopulation of Phase 3b CompLEEmment-1 Study

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Accepted: 10 August 2022 / Published online: 24 September 2022
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Abstract

Background Ribociclib plus letrozole demonstrated manageable safety and efficacy profiles in hormone receptor–positive (HR+), human epidermal growth factor receptor-2–negative (HER2–) advanced breast cancer (ABC) in the Phase 3b CompLEEmment-1 trial.

Objective To evaluate the safety and efficacy of ribociclib plus letrozole in the Italian subpopulation with HR+, HER2– ABC from the CompLEEmment-1 trial.

Patients and Methods Patients with HR+, HER2– ABC received ribociclib (600 mg/day, 3 weeks on/1 week off) plus letrozole (2.5 mg/day) while men and premenopausal women additionally received goserelin. Patients were allowed with ≤ 1 line of prior chemotherapy and an Eastern Cooperative Oncology Group performance status of ≤ 2. The primary outcome included safety and tolerability.

Results Of the 554 Italian patients, 246 (44.4 %) patients completed treatment. The reasons for treatment discontinuation included progressive disease (PD; 36.6 %), adverse events (AEs; 11.9 %), and death (1.6 %). All-grade AEs and grade ≥ 3 AEs occurred in 98.9 % and 77.8 % patients, respectively. The most common treatment-related AEs were neutropenia (73.6 %), followed by leukopenia (32.1 %), and nausea (25.3 %). The overall response rate was 28.2 % (95 % confidence interval [CI], 24.4–32.1); clinical benefit rate was 71.7 % (95 % CI, 67.7–75.4); and median time to progression was 26.7 months (95 % CI, 24.8–non-estimable). Health-related quality of life scores were maintained during treatment.

Conclusion The safety and efficacy profiles of ribociclib plus letrozole in the Italian subpopulation was found to be consistent with the CompLEEmment-1 global population result, MONALEESA-2, and MONALEESA-7 outcomes, which reaffirm ribociclib plus letrozole as the frontline treatment option in patients with HR+, HER2– ABC.

Trial Registration Number and Date of Registration NCT02941926 (30 November 2016).

1 Introduction

Hormone receptor-positive (HR+) breast cancer is the predominant subtype comprising approximately 75 % of all clinical breast cancers [1, 2]. Expression of the estrogen receptor (ER) and/or progesterone receptor (PgR) primarily leads to tumor growth and progression [3]. Although endocrine therapy (ET) has been a long-established approach for

the treatment of HR+ ABC, it is limited by the resistance developed by the patients with HR+ ABC [3–7].

The CDK4/6 inhibitor, ribociclib in combination with ET showed significantly longer progression-free survival (PFS) compared to placebo group in Phase 3 MONALEESA-2, MONALEESA-3, and MONALEESA-7 trials in patients with HR+, HER2– ABC [8–11]. In MONALEESA-3 and MONALEESA-7 trials, ribociclib in combination with fulvestrant or a nonsteroidal aromatase inhibitor or tamoxifen, demonstrated statistically significant overall survival (OS) compared to the placebo arm. These were maintained in the long-term follow-up [12, 13]. Results from the Phase 3 MONALEESA-2 trial demonstrated a statistically significant

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Key Points

In this Phase 3b CompLEEmment-1 trial, the findings are reported from the Italian population with HR+, HER2– ABC who were treated with ribociclib plus letrozole.

The safety and efficacy results from this analysis are in line with the outcomes from CompLEEmment-1 global population, MONALEESA-2, and MONALEESA-7, which further support the use of ribociclib plus letrozole as frontline therapy in HR+, HER2– ABC.

and clinically meaningful OS benefit of over 12 months for ribociclib combined with letrozole compared to letrozole alone as first-line treatment in postmenopausal women with HR+, HER2– ABC [14]. Therefore, ribociclib has shown improvement in both PFS and OS across all the three Phase 3 trials (MONALEESA-2, MONALEESA-3, and MONALEESA-7) [12–14].

The Phase 3b, CompLEEmment-1 trial is an open-label, multicenter, single-arm study intended to further evaluate the overall safety, tolerability, and efficacy of ribociclib combined with letrozole in a patient population that was larger and more diverse compared to the pivotal trials on ribociclib. A primary analysis of CompLEEmment-1 study based on 3246 patients showed a favorable safety profile for the combination therapy with respect to adverse events (AEs) and serious AEs (SAEs), consistent with that of the pivotal Phase 3 MONALEESA-2 trial results [15]. Italian patients enrolled in this study represent about 17 % of the total population (554 patients). This subgroup analysis was performed in an effort to understand the response to treatment in the large Italian subpopulation and confirm its consistency with the global population. The safety and efficacy of ribociclib in combination with letrozole in Italian patients with HR+, HER2– ABC from CompLEEmment-1 trial (NCT02941926) are reported here.

2 Methods

2.1 Study Design and Treatment

CompLEEmment-1 was an open-label, single-arm, multicenter Phase 3b study conducted to evaluate the overall safety, tolerability, and clinical efficacy of ribociclib in combination with letrozole in pre-/postmenopausal females or males with HR+, HER2– ABC, who received no prior hormonal therapy for advanced disease. The CompLEEmment-1 study

design details have been discussed in the prior publication on the global population [15].

The study comprised the core phase from first patient first visit (FPFV) to 18 months after last patient first visit (LPFV); and extension phase from 18 months after LPFV to last patient last visit (LPLV). Study treatment of the core phase was continued until disease progression, death, unacceptable toxicities, or discontinuations due to any other reason. When patients discontinued ribociclib treatment, they were discontinued from the study and censored, regardless of ET continuation. All patients were followed for 30 days after the last ribociclib dose. Transition to the extension phase happened only when the patients that were still obtaining clinical benefit at the end of core phase had no access to commercial ribociclib outside of the clinical trial, in countries where ribociclib was not approved, available, or reimbursed.

Patients received ribociclib 600 mg (3 tablets of 200 mg) orally daily on a 3 weeks on/1 week off schedule. Additionally, patients received letrozole 2.5 mg once a day on a continuous daily schedule through a 28-day cycle. Male patients and premenopausal female patients received goserelin 3.6 mg (as an injectable subcutaneous implant) once every 28 days.

Dose reduction, temporary interruption, and/or discontinuation of ribociclib therapy were permitted for the management of severe or intolerable adverse reactions. However, dose reductions were not permitted for letrozole or goserelin.

2.2 Patients

Pre-/postmenopausal female or male patients (aged ≥ 18 years) with HR+, HER2– ABC who have received ≤ 1 line of chemotherapy and no prior ET for advanced disease, were enrolled in this study. Patients with disease-free interval (DFI) > 12 months from the completion of (neo) adjuvant therapy and who had received treatment with letrozole or anastrozole for ≤ 28 days prior to enrollment were included. Patients with adequate bone marrow and organ function, and Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 were included for this study. At screening, patients needed to have QTc < 450 ms measured by Fridericia's correction and resting heart rate of ≥ 50 beats per minute.

Patients who received any prior CDK4/6 inhibitor or systemic hormonal therapy for ABC or concurrently using other anticancer therapy and patients with known history of HIV infection were excluded. Patients with central nervous system (CNS) metastases were excluded unless they had the following: (1) at least 4 weeks interval from the completion of prior therapy for CNS disease to the start of study treatment and (2) clinically stable CNS lesions at the time of study treatment initiation without having received prior steroids

and/or enzyme inducing anti-epileptic medications for the management of brain metastases for ≥ 2 weeks before study entry. Patients with clinically significant, uncontrolled heart disease and/or cardiac repolarization abnormalities, and concurrent malignancy or malignancy within 3 years prior to starting study drug (except requisitely treated basal cell or squamous cell carcinoma, non-melanomatous skin cancer; or curatively resected cervical cancer) were also excluded.

2.3 Objectives and Endpoints

CompLEEmment-1 study objectives and endpoints were previously reported by De Laurentiis et al [15]. Briefly, the primary objective of this study was to further evaluate the safety and tolerability of ribociclib in combination with letrozole in a broader population including men and postmenopausal women with HR+, HER2– ABC, who received no prior hormonal therapy for advanced disease. Safety assessments involved monitoring and recording of all AEs including grade 3/4 AEs, SAEs, and AEs leading to drug discontinuation and deaths.

The secondary objective was to evaluate the clinical efficacy of ribociclib and letrozole in the full analysis set (FAS) based on the following endpoints as defined by RECIST1.1:

- Time-to-progression (TTP) based on investigators' assessment, defined as the time from date of treatment initiation to the date of event.
- Overall response rate (ORR) for patients with measurable disease, which indicates the proportion of patients with a best overall response of complete response (CR) or partial response (PR) (ORR: CR + PR).
- Clinical benefit rate (CBR), which indicates the proportion of patients with a best overall response of CR, or PR or an overall lesion response of stable disease (SD), lasting for at least 24 weeks, as per local review (CBR: CR + PR + [SD + Non-CR/Non-PD ≥ 24 weeks]).
- Quality of life (QOL) was evaluated using the validated Functional Assessment of Cancer Therapy–Breast Cancer (FACT-B) questionnaire.

2.4 Statistical Analysis

Demographic and other baseline data including disease characteristics were summarized descriptively for the FAS in the Italian patients' subgroup. The FAS included all patients who received at least one dose of ribociclib or letrozole or goserelin in the core phase. The safety analysis was conducted on the safety set in the core phase for the Italian patients' subgroup, which included all patients who received at least one dose of ribociclib or letrozole or goserelin. The definition of safety set in the core phase is the same as for the FAS.

The primary safety variables that included AEs, SAEs, CTCAE version 4.03 grade 3/4 AEs, AEs leading to discontinuation and deaths, and AEs leading to dose reduction or interruption were summarized by count and percentage in safety set. The clinical efficacy analysis was conducted on FAS. The proportions of patients with ORR and CBR were calculated and summarized using frequency tables with their associated 2-sided exact 95% CI. The distribution of TTP was estimated using the Kaplan-Meier method.

The QOL data were collected using FACT-B questionnaire and the PRO data analysis was performed on PRO analysis set (PAS). The PAS comprised of all patients in the FAS population, for whom baseline and ≥ 1 post-baseline scores were available. Descriptive statistics were used to summarize the subscale and overall scores at each scheduled assessment time point, and change from baseline at the time of each assessment was summarized.

3 Results

3.1 Patient Characteristics and Disposition

The CompLEEmment-1 study enrolled 554 patients from Italy (overall 3246 patients) during the study period from November 30, 2016, to March 22, 2018. The cut-off date for analysis was November 8, 2019. At the end of the study, 246 (44.4 %) patients completed treatment, 103 of whom (18.6 %) entered the extension phase. The reasons for treatment discontinuation ($n = 308$, 55.6 %) included PD ($n = 203$, 36.6 %), AEs ($n = 66$, 11.9 %), physician decision ($n = 15$, 2.7 %), subject/guardian decision ($n = 12$, 2.2 %), death ($n = 9$, 1.6 %), protocol deviation ($n = 2$, 0.4 %), and lost to follow-up ($n = 1$, 0.2 %).

The median age of the patients was 58 years (range, 20–87 years); 369 (66.6 %) were aged < 65 years and 185 (33.4 %) patients were aged ≥ 65 years, 45 (8.1 %) of whom were aged ≥ 75 years. Of the 548 (98.9 %) female patients, 384 (69.3 %) were postmenopausal and 164 (29.6 %) were premenopausal women. Only 6 (1.1 %) patients in this study were men (Table 1).

Most of the patients were ER+ (99.6 %) and PgR+ (85.6 %). Among 554 patients, 331 (59.7 %) patients exhibited visceral metastases, 237 (42.8 %) had metastasis at lymph nodes, 113 (20.4 %) with bone only, 40 (7.2 %) with breast, 26 (4.7 %) with skin and 13 (2.3 %) with CNS metastases. Metastasis involving ≥ 3 sites was observed in 251 (45.3 %) patients. There were 202 (36.5 %) patients with stage IV disease at initial diagnosis, while 548 (98.9 %) had stage IV disease at the time of study entry. Among the Italian patients, 391 (70.6 %) exhibited non-de novo DFI, with 58 (10.5 %) having DFI for ≤ 12 months and 314 (56.7 %) having DFI

> 24 months. The median time since initial diagnosis of primary site was 49.1 months (Table 1).

Among the 554 patients, 386 (69.7 %) had prior antineoplastic therapy, while 168 (30.3 %) had received no prior therapy. Of all the 554 patients, 513 (92.6 %) had undergone surgery, and 264 (47.7 %) had received radiotherapy. Based on the medication in chemotherapy setting, 211 (38.1 %) patients received chemotherapy in adjuvant setting, 60 (10.8 %) patients in neoadjuvant setting, 18 (3.2 %) in palliative care, 29 (5.2 %) in therapeutic and 38 (6.9 %) in other settings. Based on the type of last therapy, 74 (13.4 %) patients received chemotherapy, 86 (15.5 %) received hormonal therapy, 108 (19.5 %) received radiotherapy and 256 (46.2 %) underwent surgery (Table S1).

3.2 Safety

During the study period, 548 (98.9 %) patients experienced any grade AEs and most patients ($n = 431$, 77.8 %) experienced grade ≥ 3 AEs. Treatment-related AE of any grade were experienced by 532 (96 %) patients and 394 (71.1 %) patients had treatment-related AEs of grade ≥ 3 severity. The most commonly observed treatment-related AEs were neutropenia ($n = 408$, 73.6 %), followed by leukopenia ($n = 178$, 32.1 %), nausea ($n = 140$, 25.3 %), asthenia ($n = 127$, 22.9 %), anemia ($n = 106$, 19.1 %), increase in ALT ($n = 75$, 13.5 %), increase in AST ($n = 56$, 10.1 %), arthralgia ($n = 67$, 12.1 %), vomiting ($n = 57$, 10.3 %), diarrhea ($n = 56$, 10.1 %), alopecia ($n = 51$, 9.2 %), fatigue ($n = 46$, 8.3 %), thrombocytopenia ($n = 45$, 8.1 %), stomatitis ($n = 40$, 7.2 %), and pruritus ($n = 35$, 6.3 %) (Fig. 1). Overall, 91 patients (16.4 %) experienced all-grade SAEs and 76 (13.7 %) patients experienced grade ≥ 3 SAEs. Among the SAEs, 30 (5.4 %) were treatment-related grade ≥ 3 . In total, 10 (1.8 %) patients experienced fatal SAEs on-treatment, 2 of which were treatment related (Table 2).

Among 38 (6.9 %) patients who died, 29 (5.2 %) deaths occurred due to breast cancer and 9 (0.2 %) deaths were caused by each of the following: cardiac arrest, cardiovascular disorder, cerebral hemorrhage, hepatic failure, legionella infection, pneumonia, pneumonitis, pulmonary embolism, and respiratory failure.

Overall, 12.6 % of all-grade AEs lead to permanent discontinuation to study treatment and among these, 7.6 % were grade ≥ 3 AEs. Treatment-related all-grade AEs were 54 (9.7 %) and among them 32 (5.8 %) were treatment-related grade ≥ 3 AEs, which led to discontinuation. Majority of the AEs ($n = 443$, 80 %) lead to dose adjustment or interruption. Treatment-related all-grade AEs were 413 (74.5 %) leading to dose adjustment or interruption, and among them 368 (66.4 %) were treatment-related grade ≥ 3 AEs (Table 2).

3.3 Efficacy

Of all the patients in the FAS, 353 (63.7 %) patients had measurable disease and 201 (36.3 %) had non-measurable disease (Table 3). In all the patients in FAS, the best overall responses as per local investigator's assessment were non-CR/non-PD and PR, observed in 165 (29.8 %) and 139 (25.1 %) patients, respectively; these were followed by SD in 138 (24.9 %) patients. Complete response was observed in 17 (3.1 %) of patients, while 27 (4.9 %) had PD. Based on the local investigator's assessment, among 353 patients with measurable disease, 138 (39.1 %) had SD while only 19 (5.4 %) had PD; CR was observed in 12 (3.4 %) patients, while PR was observed in 139 (39.4 %) patients. By investigator's assessment, ORR was 28.2 % ($n = 156$; 95 % CI, 24.4–32.1) among all Italian patients and 42.8 % ($n = 151$; 95 % CI, 37.6–48.1) among patients with measurable disease. Clinical benefit rate was 71.7 % ($n = 397$; 95 % CI, 67.7–75.4) in the overall Italian population and 68.8 % ($n = 243$; 95 % CI, 63.7–73.6) among patients with measurable disease.

Kaplan–Meier analysis of TTP with 95 % CI is summarized in Fig. 2. The median TTP was 26.7 months (95 % CI, 24.8–nonestimable) in the Italian patient population, as assessed by the local investigators.

The PAS comprised 425 female patients. The FACT-B scores as well as the overall changes in FACT-B scores from baseline until end of treatment (EOT) were assessed for individual domains, including physical, social/family, emotional and functional well-being, and additional concerns (Table S2). The FACT-B domain scores for emotional/functional well-being and other concerns were maintained till the EOT (Figs S1, S2, and S3), while for the domains like physical and social/family well-being, there was a tendency to maintain the score during treatment (Table S2). The median for time to first occurrence of a clinically relevant deterioration (≥ 7 -point decrease) in overall FACT-B score was found to be non-estimable (Fig. 3).

4 Discussion

The pivotal Phase 3 studies on CDK4/6 inhibitors, ribociclib (MONALEESA-2), palbociclib (PALOMA-2), and abemaciclib (MONARCH-3) as first-line treatment demonstrated significant improvement in PFS for their combined use with letrozole or nonsteroidal aromatase inhibitor in postmenopausal women with HR+, HER2– ABC [8, 16, 17]. The recent results from MONALEESA-2 trial showed significant survival benefit with median OS of 63.9 months for ribociclib with letrozole, compared to 51.4 months for letrozole alone (hazard ratio, 0.76; $p = 0.004$) and this treatment is now a preferred regimen for the treatment of HR+ advanced disease [14].

Table 1 Patient demographics and characteristics at baseline

	Subgroup <i>N</i> = 554
Demographic variable	
Age (years)	
Mean (SD)	57.8 (12.2)
Age category (years), <i>n</i> (%)	
< 65 years	369 (66.6)
65 to < 70 years	76 (13.7)
70 to < 75 years	64 (11.6)
≥ 75 years	45 (8.1)
Sex, <i>n</i> (%)	
Male	6 (1.1)
Race, <i>n</i> (%)	
Caucasian	525 (94.8)
Other	17 (3.1)
Native American	5 (0.9)
Asian	3 (0.5)
Unknown	3 (0.5)
Pacific Islander	1 (0.2)
Ethnicity, <i>n</i> (%)	
Other	406 (73.3)
Hispanic or Latino	69 (12.5)
Not reported	68 (12.3)
Unknown	8 (1.4)
Southeast Asian	2 (0.4)
East Asian	1 (0.2)
Body mass index (kg/m ²)	
<i>n</i>	535
Mean (SD)	25.86 (5.139)
Missing	19
Childbearing status, <i>n</i> (%)	
Able to bear children	161 (29.1)
Post-menopausal	384 (69.3)
Sterile—of childbearing age	3 (0.5)
Missing	6 (1.1)
ECOG performance status, <i>n</i> (%)	
0	426 (76.9)
1	113 (20.4)
2	14 (2.5)
3	0
4	0
Missing	1 (0.2)
Disease characteristics	
Histological grade, <i>n</i> (%)	
Well differentiated	27 (4.9)
Moderately differentiated	246 (44.4)
Poorly differentiated	122 (22.0)
Undifferentiated	4 (0.7)
Unknown	155 (28.0)

Table 1 (continued)

	Subgroup <i>N</i> = 554
Stage at initial diagnosis, <i>n</i> (%)	
0	5 (0.9)
I	83 (15.0)
II	154 (27.8)
III	107 (19.3)
IV	202 (36.5)
Unknown	1 (0.2)
Missing	2 (0.4)
Stage at time of study entry, <i>n</i> (%)	
III	6 (1.1)
IV	548 (98.9)
Time since initial diagnosis of primary site (months)	
<i>n</i>	554
Median	49.1
Time since initial diagnosis of primary site (months), <i>n</i> (%)	
≤ 3 months	131 (23.6)
> 3 and ≤ 12 months	81 (14.6)
> 12 months	342 (61.7)
Disease-free interval, <i>n</i> (%)	
De novo	163 (29.4)
Non-de novo	391 (70.6)
≤ 12 months	58 (10.5)
> 12 to ≤ 24 months	19 (3.4)
> 24 months	314 (56.7)
Types of lesions at baseline, <i>n</i> (%)	
Target only	49 (8.8)
Non-target only	201 (36.3)
Both target and non-target	304 (54.9)
Progesterone receptor status, <i>n</i> (%)	
Positive	474 (85.6)
Negative	78 (14.1)
Unknown	2 (0.4)
Current extent of disease (metastatic sites), <i>n</i> (%)	
Bone	396 (71.5)
Bone only	113 (20.4)
Breast	40 (7.2)
CNS	13 (2.3)
Visceral	331 (59.7)
Liver	154 (27.8)
Lung	238 (43.0)
Other	37 (6.7)
Skin	26 (4.7)
Lymph nodes	237 (42.8)
Others	27 (4.9)
Number of metastatic sites involved, <i>n</i> (%)	
0	2 (0.4)
1	157 (28.3)
2	144 (26.0)
3	112 (20.2)

Table 1 (continued)

	Subgroup <i>N</i> = 554
4	69 (12.5)
≥ 5	70 (12.6)

CNS central nervous system, *ECOG PS* Eastern Cooperative Oncology Group performance status, *SD* standard deviation

CompLEEmment-1 is a Phase 3b trial aimed at evaluating safety, tolerability, and clinical efficacy of ribociclib combined with letrozole in an expanded and more diverse patient population with HR+, HER2– ABC, including both men and women of any menopausal status, having ≤ 1 line of prior CT and no prior ET. The Italian population in this study is notably the largest population from any country in the CompLEEmment-1 trial, and the outcomes are consistent with the findings of the global CompLEEmment-1 study data

[15]. Because nearly one out of five patients enrolled in this trial is Italian, this subgroup analysis is adding another level of evidence on the safety and efficacy of ribociclib in this subgroup population. It further proves that the findings from this specific subgroup did not unbalance the FAS results. Among the Italian patients, most patients experienced any-grade AEs (98.9 %) with 12.6 % of AEs leading to treatment discontinuation which are comparable to the global patient population data [15]. The findings from this analysis are consistent with the safety profile for ribociclib in the MONALEESA-2 clinical trial [8]. With respect to AEs, the most commonly occurring one was neutropenia observed in 76.9 % patients in MONALEESA-2 study [8], 74.5 % in global population of CompLEEmment-1 study [15], and 73.6 % in the Italian subpopulation of CompLEEmment-1 study. The results of this analysis further support the safety and efficacy of the ribociclib and letrozole combination in Italian patients with HR+, HER2– ABC.

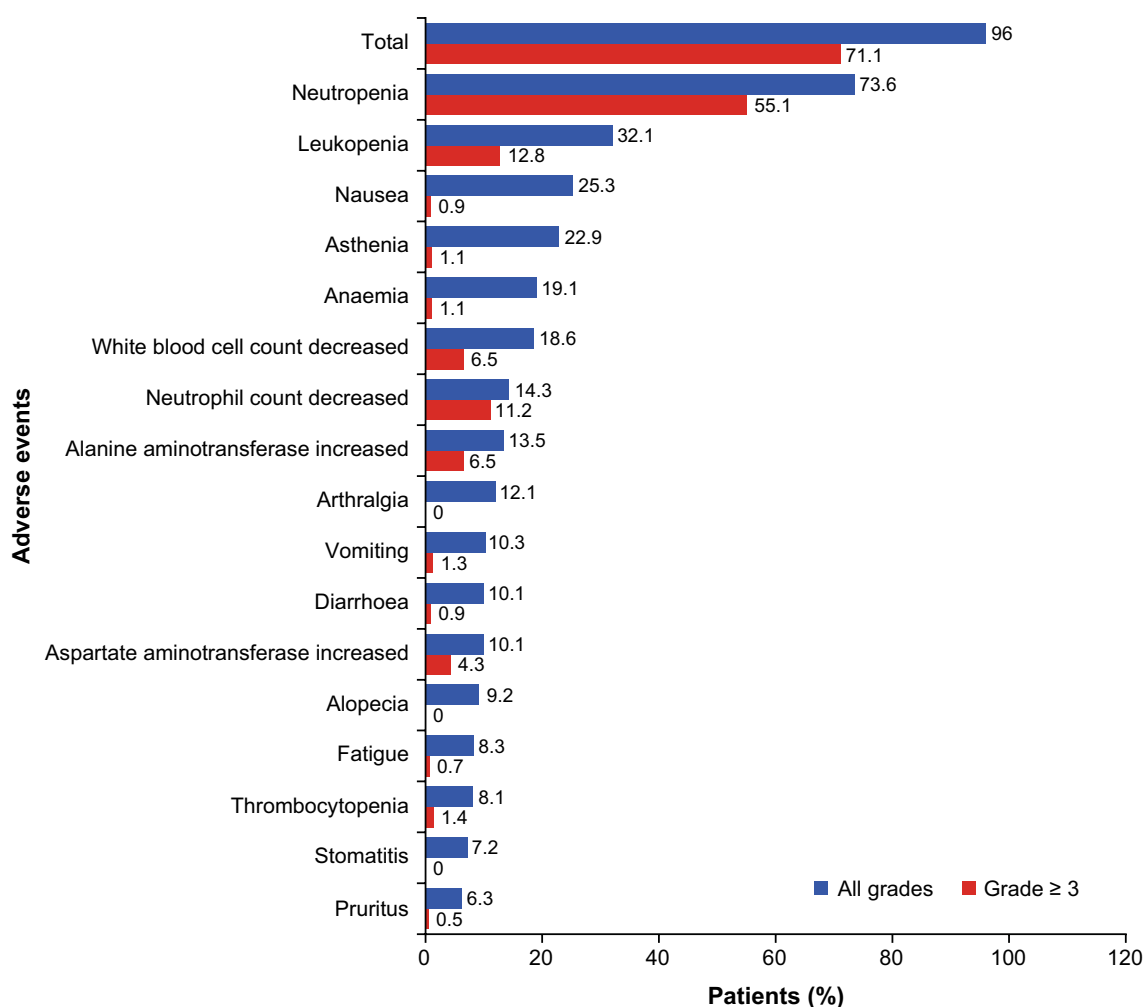
**Fig. 1** Treatment-related adverse events (> 5 %) by preferred term for subgroup

Table 2 Overview of adverse events

Category	Subgroup N = 554	
	All grades n (%)	Grade ≥3 n (%)
Adverse events	548 (98.9)	431 (77.8)
Treatment related	532 (96.0)	394 (71.1)
SAEs	91 (16.4)	76 (13.7)
Treatment related	33 (6.0)	30 (5.4)
Fatal SAEs	10 (1.8)	10 (1.8)
Treatment related	2 (0.4)	2 (0.4)
AEs leading to discontinuation	70 (12.6)	42 (7.6)
Treatment related	54 (9.7)	32 (5.8)
AEs leading to dose adjustment/interruption	443 (80.0)	385 (69.5)
Treatment related	413 (74.5)	368 (66.4)
AEs requiring additional therapy	433 (78.2)	141 (25.5)
Treatment related	245 (44.2)	78 (14.1)

AEs adverse events, SAE serious adverse event

An ORR of 28.2 % reported among all Italian patients and 42.8 % among patients with measurable disease were similar to the range reported in global patient population. Similarly, the median TTP was 27 months in both the population sets. The CBR was comparable between Italian population and global population: 71.7 % (all Italian population) versus 70.7 % (all global population) and 68.8 % versus 69.1 % among patients with measurable disease [15].

BioItaLEE, a recent Phase 3b Italian study investigating a large panel of biomarkers in the same patient setting as the MONALEESA-2, strongly support the frontline use of ribociclib plus letrozole in postmenopausal patients with HR+, HER2– ABC [18]. The ORR reported among the Italian patients with measurable disease in the ComPLEEment-1 study (42.8 %) is slightly lower than those reported in the BioItaLEE study (52.5 %) while the CBR was comparable (70.6 % in BioItaLEE population vs 68.8 % in ComPLEEment-1 Italian population). Notably, neutropenia was reported as the most commonly occurring AE (≥ grade 3) in both the trials [18]. The differences in the patients' baseline

Table 3 Best overall response as per local investigator's assessment for subgroups

	Subgroup N = 554	
	n (%)	95% CI
For all patients		
Patients with measurable disease at baseline	353 (63.7)	
Patients with non-measurable disease only at baseline	201 (36.3)	
Best overall response		
Complete response (CR)	17 (3.1)	
Partial response (PR)	139 (25.1)	
Non-CR/Non-PD	165 (29.8)	
Stable disease (SD)	138 (24.9)	
Progressive disease (PD)	27 (4.9)	
Unknown (UNK)	68 (12.3)	
Overall response rate (ORR: CR+PR)	156 (28.2)	(24.4, 32.1)
Clinical benefit rate (CBR: CR+PR+[SD+Non-CR/Non-PD ≥24 weeks])	397 (71.7)	(67.7, 75.4)
For patients with measurable disease		
Patients with measurable disease at baseline	353 (100.0)	
Best overall response		
Complete response (CR)	12 (3.4)	
Partial response (PR)	139 (39.4)	
Stable disease (SD)	138 (39.1)	
Progressive disease (PD)	19 (5.4)	
Unknown (UNK)	45 (12.7)	
Overall response rate (ORR: CR+PR)	151 (42.8)	(37.6, 48.1)
Clinical benefit rate (CBR: CR+PR+[SD ≥24 weeks])	243 (68.8)	(63.7, 73.6)

CBR clinical benefit rate, CI confidence interval, CR complete response, ORR overall response rate, PD progressive disease, PR partial response, UNK unknown

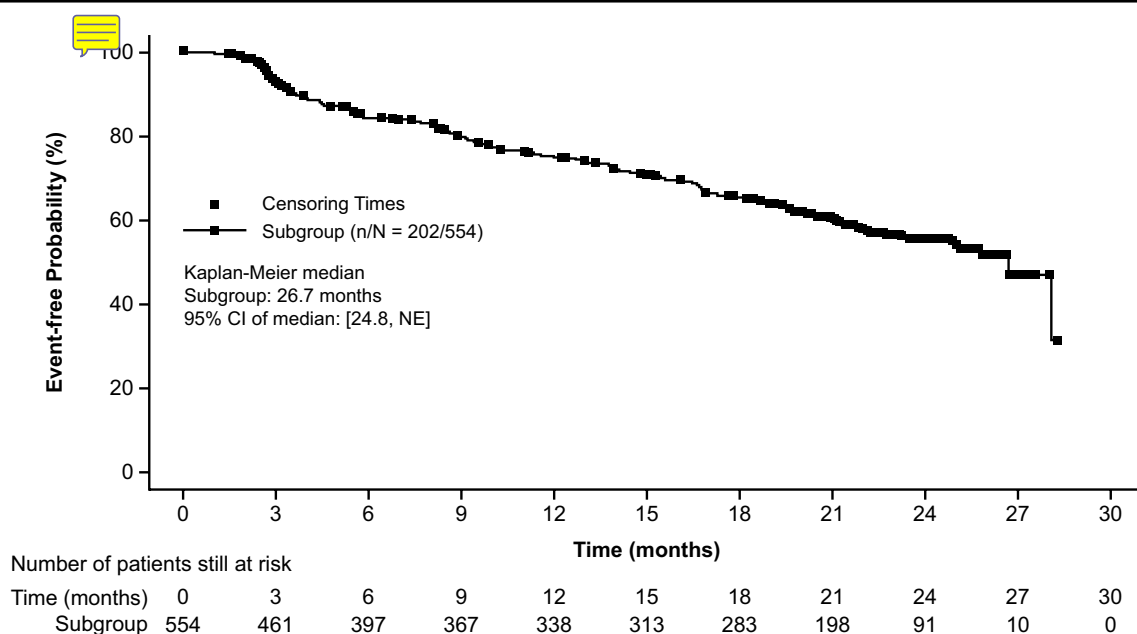
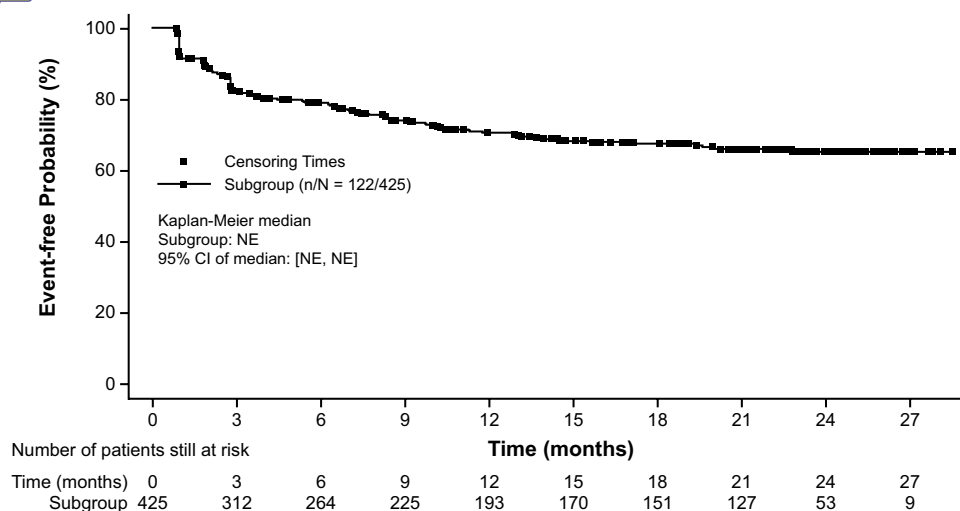


Fig. 2 Kaplan–Meier plot of time to progression as per local investigator's assessment for subgroup

Fig. 3 Kaplan–Meier plot of time to first occurrence of a clinically relevant deterioration, defined as a ≥ 7 -point decrease in FACT-B total scores (patient-reported outcomes analysis set)



characteristics between the trials should be considered when comparing the efficacy between the trials.

The compLEEment-1 trial evaluated the health-related QOL of the Italian patients through PRO measures using FACT-B questionnaire which is widely used along with EORTC QLQ-C30 questionnaire in majority of the advanced breast cancer clinical trials [19]. Based on the outcome, the FACT-B scores were maintained for emotional/functional well-being and other concerns, and closely maintained for physical and social/family well-being, until EOT. The median time to first occurrence of clinically relevant deterioration (≥ 7 -point decrease) in total FACT-B score was not estimable, thereby indicating that no deterioration of QOL was observed

during the treatment period. These findings were in line with the global data of CompLEEment-1 study and MONALEESA-2 study, in which the health-related QOL scores in the ribociclib arm were consistently maintained throughout the study [15, 20].

This study design was limited with no control or comparator arm and lacked overall survival endpoint. However, the trial being performed on the largest diverse population set, representative of a real-world setting, would add value by supporting the existing efficacy and safety profile of ribociclib combined with letrozole in patients with HR+, HER2– ABC. The results from the largest Italian subpopulation representing 17 % of the FAS population in this trial is underscored by the need to understand the treatment response in this large

subgroup and establish consistency with the outcome from global population. Overall, the study results in the Italian population further affirm the efficacy and safety of ribociclib in combination of letrozole in patients with HR+, HER2– ABC.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s11523-022-00913-x>.

Declarations

Funding This study was funded by Novartis Pharmaceuticals Corporation.

Conflict of interest Michelino De Laurentiis participated in the advisory board and received grants, consulting fees and honoraria from Novartis, Roche, MSD, Astra Zeneca, Daiichi Sankyo, Seagen, Eli Lilly, and Pfizer. Manuelita Mazza participated in the advisory board and received grants, consulting fees and honoraria from Novartis, Pfizer, Astra Zeneca, Eli Lilly, Gentili, and Roche. Mauro Mansutti participated in the advisory board of Amgen, Astra Zeneca, Eli Lilly, Gentili, MSD Italia, Novartis, Pfizer, Roche; honoraria from Pierre Fabre; reimbursement of travel or accommodation expenses from Eisai, Novartis, Pfizer, Pierre Fabre, Roche. Zelmira Ballatore received honoraria from Ipsen, Novartis, Roche. Rosalba Torrisi received honoraria from Astra Zeneca, Eisai, Pfizer, Eli Lilly, and Gentili. Rita De Sanctis Novartis, Amgen, Kyowa Kirin, and Eisai. Alberto Zambelli participated in the advisory board of Novartis, Pfizer, Astra Zeneca, Daiichi Sankyo, MSD, Eli Lilly; received honoraria from Novartis, Pfizer, Astra Zeneca, Daiichi Sankyo, MSD, Eli Lilly, Exact Sciences. Antonella Ferro received personal fees from Novartis and Eli Lilly. Daniele Generali participated in advisory board for Lilly, Novartis, Pierre Fabre; received honoraria from Novartis, Pfizer, Lilly, Astra Zeneca, ESAI, Istituto Gentili; reimbursement of travel or accommodation expenses from Novartis, Lilly, and Pierre-Febre. Patrizia Vici participated in advisory board for Novartis, Eisai; and received honoraria from Pfizer, Novartis, Gentili, Lilly, ESAI, Roche. Paolo Marchetti received honoraria from Roche, BMS, MSD, Novartis, Pfizer, Pierre Fabre; reimbursement support for congress attendance from BMS, Roche, Pierre Fabre; received grants to institution from Roche, BMS, Pfizer, Incyte, Novartis, Takeda, MSD, Pierre Fabre. Simon Spazzapan participated in the advisory board of Novartis, Astra Zeneca, Daiichi Sankyo and received honoraria from Novartis, Pfizer, Astra Zeneca, Daiichi Sankyo, MSD, Eli Lilly. Antonio Frassoldati participated in the advisory board and received personal fees from Novartis, Astra Zeneca, Pfizer, Lilly, Roche, Daiichi, Seagen, Amgen. Maria Giuseppina Sarobba participated in the advisory board of Novartis, Pierre Fabre, MSD, and received honoraria from Novartis, Pfizer, Lilly, Astra Zeneca, MSD, Astellas. Donatella Grasso is employed by Novartis. Claudio Zamagni has received honoraria for consulting or advisory roles from Astra Zeneca, Eisai, Novartis, Pfizer, PharmaMar, Pierre Fabre, and Roche; research funding from AbbVie, Array BioPharma, Astra Zeneca, Celgene, Medivation, Morphotek, Novartis, Pfizer, Roche, and Roche/Genentech; reimbursement for travel, accommodations, or expenses from Celgene, Novartis, Pierre Fabre, and Roche. Roberta Caputo, Riccardo Masetti, Andrea Michelotti, Luigi Coltelli, Alessandra Fabi, and Alberto Ballestrero declared no conflict of interest.

Data availability The data that support the findings of this study are available from Novartis Pharmaceuticals Corporation, but restrictions apply to the availability of these data (<https://www.novartisclinicaltrials.com/TrialConnectWeb/home.nov>). However, data are available from the authors upon reasonable request and with permission of Novartis Pharmaceuticals Corporation.

Ethics Approval The study was reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board before study commencement for each center and was conducted in accordance with the in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Harmonized Tripartite Guidelines for Good Clinical Practice, applicable local regulations, and the ethical principles laid down in the Declaration of Helsinki. All patients provided written informed consent prior to participation in the study.

Consent to participate Written informed consent was obtained from all patients.

Author Contributions All authors critically reviewed, provided feedback at each stage of the manuscript, approved the final version and agreed to be accountable for all aspects of the work.

Acknowledgments We thank all patients and investigators involved in the study. Medical writing assistance was provided by Moumita Samanta, PhD from Novartis Pharmaceuticals Corporation, India.


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References

1. Arnesen S, Blanchard Z, Williams MM, Berrett KC, Li Z, Oesterreich S, et al. Estrogen receptor alpha mutations in breast cancer cells cause gene expression changes through constant activity and secondary effects. *Can Res*. 2021;81(3):539–51.
2. Burris HA 3rd. Ribociclib for the treatment of hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer. *Expert Rev Anticancer Ther*. 2018;18(3):201–13.
3. Baselga J, Campone M, Piccart M, Burris HA 3rd, Rugo HS, Sahmoud T, et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. *N Engl J Med*. 2012;366(6):520–9.
4. Johnston SR. New strategies in estrogen receptor-positive breast cancer. *Clin Cancer Res*. 2010;16(7):1979–87.
5. Mauri D, Pavlidis N, Polyzos NP, Ioannidis JP. Survival with aromatase inhibitors and inactivators versus standard hormonal therapy in advanced breast cancer: meta-analysis. *J Natl Cancer Inst*. 2006;98(18):1285–91.
6. Smith IE, Dowsett M. Aromatase inhibitors in breast cancer. *N Engl J Med*. 2003;348(24):2431–42.
7. Mouridsen H, Sun Y, Gershanovich M, Perez-Carrion R, Becquart D, Chaudri-Ross HA, et al. Superiority of letrozole to tamoxifen in the first-line treatment of advanced breast cancer: evidence from metastatic subgroups and a test of functional ability. *Oncologist*. 2004;9(5):489–96.

8. Hortobagyi GN, Stemmer SM, Burris HA, Yap YS, Sonke GS, Paluch-Shimon S, et al. Updated results from MONALEESA-2, a Phase III trial of first-line ribociclib plus letrozole versus placebo plus letrozole in hormone receptor-positive, HER2-negative advanced breast cancer. *Ann Oncol.* 2018;29(7):1541–7.
9. Im SA, Lu YS, Bardia A, Harbeck N, Colleoni M, Franke F, et al. Overall survival with ribociclib plus endocrine therapy in breast cancer. *N Engl J Med.* 2019;381(4):307–16.
10. Tripathy D, Im SA, Colleoni M, Franke F, Bardia A, Harbeck N, et al. Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomised Phase 3 trial. *Lancet Oncol.* 2018;19(7):904–15.
11. Yardley DA, Hart L, Favret A, Blau S, Diab S, Richards D, et al. Efficacy and safety of Ribociclib with Letrozole in US patients enrolled in the MONALEESA-2 study. *Clin Breast Cancer.* 2019;19(4):268–77.
12. Slamon DJ, Neven P, Chia S, Jerusalem G, De Laurentiis M, Im S, et al. Ribociclib plus fulvestrant for postmenopausal women with hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer in the Phase III randomized MONALEESA-3 trial: updated overall survival. *Ann Oncol.* 2021;32(8):1015–24.
13. Lu YS, Im SA, Colleoni M, Franke F, Bardia A, Cardoso F, et al. Updated overall survival of ribociclib plus endocrine therapy versus endocrine therapy alone in pre- and perimenopausal patients with HR+/HER2- advanced breast cancer in MONALEESA-7: a Phase III randomized clinical trial. *Clin Cancer Res.* 2022;28(5):851–9.
14. Hortobagyi GN, Stemmer SM, Burris HA, Yap YS, Sonke GS, Hart L, et al. Overall survival with ribociclib plus letrozole in advanced breast cancer. *N Engl J Med.* 2022;386(10):942–50.
15. De Laurentiis M, Borstnar S, Campone M, Warner E, Bofill JS, Jacot W, et al. Full population results from the core Phase of CompLEement-1, a Phase 3b study of ribociclib plus letrozole as first-line therapy for advanced breast cancer in an expanded population. *Breast cancer research and treatment. Breast Cancer Res Treat.* 2021;189(3):689–699.
16. Finn RS, Martin M, Rugo HS, Jones S, Im SA, Gelmon K, et al. Palbociclib and letrozole in advanced breast cancer. *N Engl J Med.* 2016;375(20):1925–36.
17. Johnston S, Martin M, Di Leo A, Im SA, Awada A, Forrester T, et al. MONARCH 3 final PFS: a randomized study of abemaciclib as initial therapy for advanced breast cancer. *NPJ Breast Cancer.* 2019;5:5.
18. De Laurentiis M, Puglisi F, Del Mastro L, Colleoni M, Montemurro F, Bianchi G, et al. Efficacy and safety of first-line Ribociclib (RIB) combined with Letrozole (LET) in postmenopausal patients with hormone receptor-positive (HR+), human epidermal growth factor receptor-2-negative (HER2-) advanced breast cancer (ABC): Results from Phase IIb BioItaLEE study. *Associazione Italiana di Oncologia Medica 2021; Italy.*
19. Krohe M, Hao Y, Lamoureux RE, Galipeau N, Globe D, Foley C, et al. Patient-reported outcomes in metastatic breast cancer: a review of industry-sponsored clinical trials. *Breast Cancer Basic Clin Res.* 2016;10:93–102.
20. Verma S, O'Shaughnessy J, Burris HA, Campone M, Alba E, Chandiwna D, et al. Health-related quality of life of postmenopausal women with hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer treated with ribociclib + letrozole: results from MONALEESA-2. *Breast Cancer Res Treat.* 2018;170(3):535–45.

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