research article

Ribociclib plus letrozole in patients with hormone receptor-positive, HER2-negative advanced breast cancer with no prior endocrine therapy: subgroup safety analysis from the phase 3b CompLEEment-1 trial

Simona Borstnar[1], Marketa Palacova[2], Aleksandra Łacko[3], Constanta Timcheva[4], Einav Nili Gal-Yam[5], Konstantinos Papazisis[6], Juraj Beniak[7], Pavol Kudela[8], Gábor Rubovszky[9]

[1] Department of Medical Oncology, Institute of Oncology Ljubljana, Ljubljana, Slovenia
[2] Clinic of Comprehensive Cancer Care, Masaryk Memorial Cancer Institute, Brno, Czech Republic
[3] Department of Clinical Oncology, Wroclaw University of Medicine, Wrocław, Poland, and Breast Unit, Lower Silesian Oncology Centre, Wroclaw, Poland
[4] Medical Oncology Clinic, Multiprofile Hospital for Active Treatment "Nadezhda" Sofia, Sofia, Bulgaria
[5] Talpiot medical leadership program, Institute of Oncology, Chaim Sheba Medical Center, Tel-Hashomer; affiliated to the Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel
[6] Euromedica General Clinic of Thessaloniki, Thessaloniki, Greece
[7] Regional Cancer Center, Poprad, Slovakia
[8] Novartis Slovakia s.r.o., Bratislava, Slovakia
[9] Department of Oncological Internal Medicine and Clinical Pharmacology, National Institute of Oncology, Budapest, Hungary

Radiol Oncol 2022; 56(2): 238-247.

Received 25 February 2022
Accepted 8 April 2022

Correspondence to: Simona Borštnar, M.D., Ph.D., Department of Medical Oncology, Institute of Oncology Ljubljana, Ljubljana, Slovenia. E-mail: sborstnar@onko-i.si and Gábor Rubovszky, Department of Oncological Internal Medicine and Clinical Pharmacology, National Institute of Oncology, Budapest, Hungary. E-mail: ruga@freemail.hu

Disclosure: Dr. Simona Borstnar reports receiving consultancy fees and/or lecture fees from Amgen, Astra Zeneca, Ewopharma, Krka, Eli Lilly, Novartis, Pfizer and Roche. Dr. Marketa Palacova reports receiving advisory role fees from Roche and Pierre Fabre, and lecture honoraria from Pfizer, Eli Lilly, Roche and Astra Zeneca. Dr. Aleksandra Łacko reports receiving research funding from Roche, MSD, AstraZeneca, Eli Lilly, Novartis, receiving consultancy and advisory boards fees from Roche, AstraZeneca, Novartis, Eli Lilly, GlaxoSmithKline, Pfizer, Mylan, Exact Sciences, Teva, receiving fees for non-CME services received directly from commercial interest or their agents from Roche, Novartis, Eli Lilly, Egis, Pfizer, Alvogen, Mylan, AstraZeneca. Prof. Costanta Timcheva reports receiving research funding from Novartis, Roche, Merck, AstraZeneca, and Pfizer, and advisory role fees from Astellas, Servier, Pfizer, and lecture honoraria from Roche, Novartis, BMS, AstraZeneca, Astellas, Servier, Pfizer, and Ewopharma. Dr. Einav Nili Gal-Yam reports receiving consultancy fees and honoraria from Novartis, Roche, MSD, Pfizer and Eli-Lilly, and travel support from Roche, Pfizer and Novartis. Dr. Konstantinos Papazisis reports receiving lecture fees and advisory board fees from Novartis, Roche, MSD, GlaxoSmithKline and travel support from Roche and MSD. Dr. Juraj Beniak reports receiving consultancy and lecture fees from Novartis, Roche, Eli Lilly, Pfizer, Astra Zeneca, Sanofi, Pierre Fabre and travel support from Sanofi. Dr. Pavol Kudela reports being employed by Novartis. Dr. Gabor Rubovszky reports receiving consultancy fees or honoraria from Amgen, Lilly, Novartis, Pfizer, Roche, and Swixx BioPharma.

Background. The CDK4/6 inhibitor, ribociclib in combination with endocrine therapy significantly improved progression-free survival in the first line setting in post-menopausal patients with HR+/HER2− advanced breast cancer (ABC) in a pivotal phase 3, placebo-controlled trial (MONALEESA-2) and demonstrated superior overall survival in premenopausal patients with HR+/HER2− ABC (MONALEESA-7). The multinational, phase 3b, CompLEEment-1 trial, which assessed the safety and efficacy of ribociclib plus letrozole in a broader population of patients who have not received prior endocrine therapy for advanced disease, is the largest phase 3 clinical trial to date to evaluate the safety and efficacy of a CDK4/6 inhibitor. We report a subanalysis of data from patients (N = 339) enrolled in the central and south European countries of the SERCE (Southern Europe, RUC, Central Europe) cluster of CompLEEment-1.

Patients and methods. Men and women of any menopausal status with HR+/HER2− ABC received once-daily oral ribociclib 600 mg (3-weeks on/1-week-off), plus letrozole 2.5 mg continuously. Men/premenopausal women also received a GnRH-agonist. The primary outcome was the number of patients with adverse events (AEs) over a timeframe of approximately 36 months. Time-to-progression, overall response rate, and clinical benefit rate were also measured.
Results. Safety results in the SERCE subgroup were consistent with those in the pivotal clinical trials of ribociclib in combination with endocrine therapy. Treatment-related AEs leading to dose adjustments/interruption occurred in 63.1% of patients but led to treatment discontinuation in only 10.6%. The most common treatment-related AEs of grade ≥ 3 were neutropenia and transaminase elevations. There were no fatal treatment-related events.
Conclusions. These findings from the SERCE subgroup support the safety and manageable tolerability of ribociclib in a broad range of patients with HR+/HER2− ABC more representative of patients in real-world clinical practice.

Key words: CDK4/6 inhibitor; ribociclib; HR+; HER2−; advanced breast cancer; CompLEEment-1 trial

Introduction

Among females, breast cancer is the most frequently diagnosed cancer in all regions of the world, with the exception of Eastern Africa, and is one of the leading causes of cancer deaths globally.[1] Breast cancer accounted for over two million new cases (11.6% of cancer diagnoses globally) and over 626,000 deaths (6.6% of cancer deaths globally) in 2018.[2] Male breast cancer is a much rarer malignancy, accounting for less than 1% of all breast cancer diagnoses, and with an incidence of less than 1% in men.[3]

Despite advances in the understanding of the pathogenesis of breast cancer that has led to improvements in the management of advanced breast cancer, it remains a serious and incurable disease, affecting pre, peri and postmenopausal women, as well as men, across a range of comorbidities, differing functional status and quality of life (QoL). Breast cancer is a heterogeneous disease that features a number of distinct histological, intrinsic molecular, and clinical subtypes differentiated by gene profiles, and also by estrogen, progesterone, and HER2 receptors as surrogate markers, all with prognostic and predictive significance.[4] Hereditary factors may also influence treatment.

Although hormone receptor-positive (HR+) and human epidermal growth factor receptor-negative (HER2−) breast cancer is the most common form of breast cancer, with the best survival pattern overall, HR+/HER2− status is associated with poorer survival in advanced-stage disease.[5] Endocrine therapy is recommended by major international treatment guidelines as first-line treatment for the majority of patients with advanced breast cancer.[6-9]

Third-generation aromatase inhibitors such as anastrozole, letrozole, and exemestane were, until recently, considered standard-of-care for first-line endocrine therapy, demonstrating improved time to treatment progression and enhanced survival duration and a more acceptable tolerability profile than older endocrine agents such as tamoxifen.[8,9] Another endocrine therapy, the selective estrogen receptor (ER) degrader, fulvestrant, has been shown to significantly improve progression-free survival (PFS) and duration of response compared with anastrozole in endocrine therapy-naïve HR+ locally-advanced or metastatic breast cancer patients.[10]

Breast cancer recurrence and the refractory nature of advanced disease remain a major clinical challenge, and new therapeutic approaches to delay the development of endocrine resistance across the diversity of patient populations with advanced breast cancer are required. A key mechanism for the development of endocrine resistance is understood to involve interactions between the estrogen receptor and growth factor receptor signaling mediated by the phosphatidylinositol-3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) pathway, the mitogen-activated protein kinase (MAPK) pathway, or the cyclin D1/cyclin-dependent kinase (CDK)-retinoblastoma tumor suppressor (Rb) cell cycle regulation pathway.[11-13] CDK4/6 overexpression, which is regularly observed in HR+ breast cancer, is a key mediator of endocrine resistance.[14]

An increasing understanding of the role of the CDK 4 and 6 pathway in the cell cycle regulation and downstream signaling responsible for overproliferation of cancer cells has resulted in the development of a number of agents that target the CDK4/6/Rb pathway.[11-14] CDK4/6 inhibitors have become established as important targeted agents for cancer treatment,[7,9] and their use to inhibit cell-cycle progression been shown to be an effective therapeutic strategy in HR+ breast cancer, with the potential of overcoming or delaying endocrine resistance.[15-17]

Currently, three CDK4/6 inhibitors have been approved for the treatment of HR+/HER2− advanced breast cancer: abemaciclib (LY-2835219; Eli Lilly), palbociclib (PD-0332991; Pfizer), and ribociclib (LEE011; Novartis). These oral, highly selective CDK inhibitors represent an important therapeutic development in the treatment of breast cancer.

Ribociclib is an orally bioavailable selective small-molecule inhibitor of CDK4/6 that acts by binding to the adenosine triphosphate (ATP)-binding cleft of CDK4 and CDK6.[18] The MONALEESA (Mammary Oncology Assessment of LEE011's Efficacy and Safety) trials (MONALEESA-2, MONALEESA-3, and MONALEESA-7)[17,19-21] were designed to investigate the use of ribociclib in a variety of different clinical breast cancer settings.

In the pivotal phase 3, double-blind, placebo-controlled MONALEESA-2 trial in the first-line setting in postmenopausal patients with HR+/HER2- advanced breast cancer, ribociclib plus letrozole in combination with endocrine therapy significantly improved PFS and overall survival (OS) compared with placebo plus letrozole.[17,22]

Subsequent trials demonstrated significant improvements in PFS and OS when ribociclib was used in combination with fulvestrant (postmenopausal patients with advanced breast cancer who were treatment naïve or had received prior endocrine therapy in the advanced setting or with progression during or within 12 months after finishing adjuvant endocrine therapy) or in combination with oral tamoxifen or a nonsteroidal aromatase inhibitor (pre/perimenopausal women with ovarian function suppression with the gonadotropin-releasing hormone (GnRH) agonist goserelin).[17,19-21]

A recent analysis of data from MONALEESA-7 showed that ribociclib in combination with endocrine therapy clinically and statistically significantly prolonged OS compared with endocrine therapy alone in premenopausal patients with HR+/HER2- advanced breast cancer.[23] After a median of 53.5 months of follow-up, the median OS was 58.7 versus 48.0 months (HR, 0.763; 95% CI 0.608–0.956) for ribociclib plus endocrine therapy versus endocrine therapy alone, which translates to a 24% reduction in relative risk of death related to the CDK4/6 inhibitor. This is the first time that adding a CDK4/6 inhibitor (or another targeted agent) to endocrine therapy has been shown to significantly improve OS.

Similarly, ribociclib plus fulvestrant significantly improved OS compared with fulvestrant plus placebo in postmenopausal patients in the MONALEESA-3 trial.[24] After a median follow-up of 39.4 months, the median OS was not reached in the ribociclib plus fulvestrant group and 40.0 months in the fulvestrant plus placebo group (hazard ratio [HR] 0.724, p = 0.00455). The advantage in OS was consistent across all patient subgroups and, together with the results of MONALEESA-7, confirm the benefit of ribociclib in combination with multiple treatment combinations in pre- and postmenopausal patients with HR2+, HER2−, advanced breast cancer.

Indeed, the ongoing MONALEESA clinical trials program has consistently demonstrated the clinical utility of ribociclib as an effective agent with a predictable and manageable safety profile in combination therapy regimens for advanced breast cancer.[19-21]

The multinational, phase 3b, CompLEEment-1 trial (ClinicalTrials.gov NCT02941926) was designed to assess the safety and efficacy of ribociclib plus letrozole in a broader patient population than the individual MONALEESA trials.[25] The CompLEEment-1 study enrolled a large number of patients under a study protocol with broad inclusion criteria that allowed the enrolment of premenopausal women and males and permitted the receipt of up to one line of chemotherapy in the advanced setting prior to CDK therapy. Patients with central nervous system metastases and with an ECOG performance status of 2 were also eligible, with the result that the study population was more representative of real-world clinical practice.

The ribociclib plus letrozole regimen in the ribociclib arm of MONALEESA-2 was identical to that of CompLEEment-1, with the exception that men and premenopausal women in CompLEEment-1 also received a GnRH-agonist, as in MONALEESA-7 (MONALEESA-2 only enrolled postmenopausal women).

Patients received once-daily oral treatment with ribociclib 600 mg in a 3-weeks on/1-week-off regimen, plus letrozole 2.5 mg continuously. Men and premenopausal women also received a GnRH-agonist [goserelin 3.6 mg as a subcutaneous implant or leuprolide (leuprorelin) 7.5 mg as an intramuscular depot injection] once every 28 days. Treatment was continued until disease progression or death.

A total of 3,246 patients were enrolled and treated between November 30, 2016, and March 22, 2018, at 508 study locations throughout North and South America, Europe, Asia, South-East Asia, Israel, Russia, and the Middle East (Appendix 1). The estimated study completion date was May 2021; the data cut-off date for this analysis was November 8, 2019.

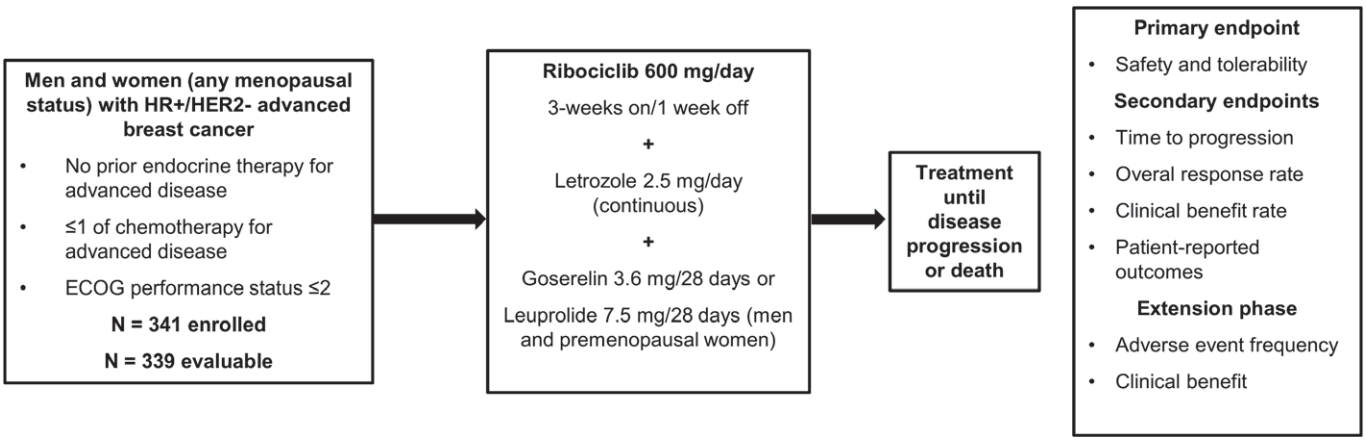

FIGURE 1. Trial Design of CompLEEment-1 showing patients enrolled in central and south European countries of the SERCE cluster.

SERCE = Southern Europe, RUC, Central Europe Countries; ECOG = Eastern Cooperative Oncology Group; HER2− = human epidermal growth factor receptor-2-negative; HR+ = hormone receptor-positive

Results from the overall CompLEEment-1 patient population demonstrated the safety, tolerability, and efficacy of ribociclib plus letrozole in this large and diverse cohort of patients with HR+/HER2− advanced breast cancer, with a safety profile consistent with the pivotal ribociclib trials and no new safety signals.[26] The median time to progression (TTP) was 27.1 months, and the clinical benefit rate (CBR) in patients with measurable disease at baseline was 69.1% and the median PFS was 26.7 months.[26] The quality of life of patients was maintained throughout treatment.

Eight countries from central and south European countries of the SERCE cluster took part in the CompLEEment-1 trial: Bulgaria, Czech Republic, Greece, Hungary, Israel, Poland, Slovakia, and Slovenia.

This paper presents a subanalysis of data from patients enrolled in the SERCE countries involved in CompLEEment-1. The aim of our subanalysis was to uncover a possible difference in the tolerability of the drug in our geographical group compared to global data. Possible differences could be expressed in the reporting of the frequency and grade of adverse effects by patients.

Patients and methods

The CompLEEment-1 trial (ClinicalTrials.gov Identifier NCT02941926) is a phase 3b, single-arm, open-label, multicenter, international study to assess the safety and efficacy of ribociclib plus letrozole in men and women of any menopausal status with HR+/HER2− advanced breast cancer who have not received prior endocrine therapy for advanced disease.

The primary aim of the study is to further evaluate the overall safety and tolerability of the combination of ribociclib with letrozole in men and pre/postmenopausal women with HR+/HER2− advanced breast cancer. Secondary endpoints are to investigate tolerability and QoL and to generate safety and clinical efficacy data in a broader patient population than that of MONALEESA-2, i.e., one that also includes pre-menopausal women; men with HR+ advanced breast cancer; patients with 1 prior line of chemotherapy for advanced disease; patients with ECOG performance status of 2; patients without a clear target lesion to be followed (i.e., no measurable or bone lytic lesions).

Patients received once-daily oral treatment with ribociclib 600 mg in a 3-weeks on/1-week-off regimen, plus letrozole 2.5 mg continuously. Men and premenopausal women also received a GnRH-agonist [goserelin 3.6 mg as a subcutaneous implant or leuprolide (leuprorelin) 7.5 mg as an intramuscular depot injection] once every 28 days. Treatment was continued until disease progression or death.

The trial design is shown in Figure 1.

Outcome measures

The primary outcome measures consisted of the number of participants with adverse events (AEs) over a timeframe of approximately 36 months, as a measure of safety and tolerability. Secondary outcome measures included: Time to progression

(TTP); Overall response rate (ORR); and CBR. ORR was defined as the proportion of patients with a complete response (CR) or partial response (PR) and CBR was defined with proportion of patients wit CR, PR or had stable disease (SD) for 6 months or more. Patient-reported outcomes (PRO) were also a secondary outcome measure in CompLEEment-1. However, PRO data were not available for this analysis.

The clinical impact of hepatobiliary events, neutropenia events, and QT prolongation were also analyzed. Patients were to be followed up until discontinuation of ribociclib, regardless of the reason.

The number of participants with AEs and the percentage of patients with investigator-assessed clinical benefit will also be measured during an extension phase of approximately 30 months.

Statistical analysis

The primary endpoint of safety/tolerability (number [%] of AEs, grade 3/4 AEs, and SAEs, AESI and AEs leading to treatment discontinuation and deaths, and AEs leading to dose reduction or dose interruption) was summarized descriptively in the safety analysis set.

The other secondary endpoints of ORR and CBR were summarized using descriptive statistics (N [%]) combined with 2-sided exact binomial 95% Cis.

Eligibility criteria

Men and pre/postmenopausal women with locally advanced or metastatic HR+/HER2− breast cancer not amenable to curative therapy and with no prior endocrine therapy for advanced disease were eligible for the study. Patients had an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2, had received ≤ 1 line of chemotherapy for advanced disease, and had a disease-free interval (DFI) greater than 12 months from completion of (neo)adjuvant therapy if treatment included a nonsteroidal aromatase inhibitor. Adequate bone marrow and organ function were required, and a QT interval corrected using Fridericia's formula (QTcF) of < 450 ms and a resting heart rate of ≥ 50 bpm at screening.

Patients were excluded if they had received prior treatment with a CDK4/6 inhibitor and/or systemic hormonal therapy for advanced breast cancer. Also excluded were concurrent malignancy, or malignancy ≤ 3 years prior to starting study drug (except adequately treated basal or squamous cell carcinoma, nonmelanoma skin cancer, or curatively resected cervical cancer), central nervous system metastases, unless lesions were clinically stable for ≥ 4 weeks, clinically significant heart disease and/or recent cardiac events (e.g., uncontrolled hypertension), and/or gastrointestinal impairment or disease that might significantly alter study drug absorption.

TABLE 1. Baseline demographic and clinical characteristics of patients in the SERCE subgroup of CompLEEment-1*

Variable	*N* = 339
Age, years	58.0 (24-88)
< 65	228 (67.3)
≥ 65	111 (32.7)
Gender	
Female	335 (98.8)
Male	4 (1.2)
Child-bearing status	
Able to bear children	80 (23.6)
Postmenopausal	241 (71.1)
Sterile – of child-bearing age	14 (4.1)
Unknown	4 (1.2)
Race	
Caucasian	330 (97.3)
Black	2 (0.6)
Other	4 (1.2)
Unknown	3 (0.9)
ECOG performance status	
0	208 (61.4)
1	119 (35.1)
2	12 (3.5)
3 or 4	0
BMI, kg/m^2	26.0 (16.1–48.4)

* Unless otherwise stated, data are median (range) or no. (%)
BMI = body mass index; ECOG = Eastern Cooperative Oncology Group

Ethical consideration

All procedures performed in studies involving human participants were in accordance with the ethical standards of the individual institutional research committees and with the 1964 Helsinki declaration and its later amendments. Informed consent was obtained from all individual participants included in the study.

TABLE 2. Disease history for patients in the SERCE subgroup of CompLEEment-1

Variable	N = 339 No. (%)
Histological grade	
Well-differentiated	29 (8.6)
Moderately differentiated	165 (48.7)
Poorly differentiated	76 (22.4)
Undifferentiated	5 (1.5)
Unknown	64 (18.9)
Disease stage at study entry	
II	1 (0.3)
III	5 (1.5)
IV	333 (98.2)
Time since diagnosis of primary site, median (range) months	33.7 (0.3-401.9)
≤ 3	72 (21.2)
> 3 and ≤ 12	53 (15.6)
> 12	213 (62.8)
Missing	1 (0.3)
Disease-free interval	
Newly-diagnosed disease	110 (32.4)
Existing disease	228 (67.3)
≤ 12 months	26 (7.7)
> 12 to ≤ 24 months	19 (5.6)
> 24 months	183 (54.0)
Missing	1 (0.3)
Types of lesions at baseline	
Target only	27 (8.0)
Non-target only	106 (31.3)
Both target and non-target	206 (60.8)
Extent of metastatic disease	
Bone	254 (74.9)
Bone only	75 (22.1)
Breast	23 (6.8)
Central nervous system	2 (0.6)
Visceral	214 (63.1)
Skin	14 (4.1)
Lymph nodes	108 (31.9)
Other	13 (3.8)
Number of metastatic sites	
1	103 (30.4)
2	105 (31.0)
≥ 3	131 (38.7)

Results

Patient characteristics and disposition

A total of 339 of the 341 patients comprising the SERCE patient population were available for the subgroup analysis. Patient characteristics at baseline for the SERCE patient population are shown in Table 1. The breast was the primary site of cancer for all patients in the SERCE population. Progesterone receptor status was positive in 82.3% of patients. One patient had HER2+ disease and two patients ER− disease. Ninety-eight percent of patients had metastatic disease at study entry. One hundred and ten patients (32.4%) had *de novo* (newly diagnosed) disease and 228 (67.3%) had recurrent disease. The disease-free interval was of greater than 12 months duration in 59.6% of patients with recurring disease.

The median follow-up duration was 17.5 months; 138 patients completed treatment, of whom 98 patients entered the Extension Phase of the study. Two-hundred-and-one patients discontinued treatment, primarily as a result of progressive disease (126 patients), AEs (N = 41), patient or guardian decision (N = 18), protocol deviation (N = 6), death (N = 6), physician decision (N = 2), lost to follow-up (N = 1) or technical issues (N = 1).

The disease history for the SERCE subgroup is shown in Table 2. The majority of the SERCE patient population presented with well-differentiated or moderately-differentiated histological grade disease. In almost a third of patients, the disease was primarily metastatic. In more than half of the patients (54%), the disease-free interval was > 24 months. Thirty-nine percent of patients had 3 or more metastatic sites, and visceral metastases were present in 63% of patients.

Safety

A summary of AEs, including serious AEs, AEs leading to discontinuation or requiring dose adjustments, dose interruption, or additional therapy, and individual AEs occurring in ≥ 10% of patients is presented in Table 3. A total of 332 patients (97.9%) experienced an AE, which was grade ≥ 3 in 238 patients (70.2%). AEs were considered to be treatment-related in 322 patients (grade ≥ 3 in 211 patients). Treatment-related AEs led to dose adjustments or interruption in 63.1% of patients. However, treatment-related AEs that led to treatment discontinuation occurred in only 10.6% of patients. There were no fatal treatment-related events.

TABLE 3. Summary of adverse events for patients (N = 339) in the SERCE subgroup of CompLEEment-1. Safety set in the core phase

Event	All grades No. (%)	Grade ≥ 3 No. (%)
Any adverse event	332 (97.9)	238 (70.2)
Treatment-related	322 (95.0)	211 (62.2)
Serious adverse event	62 (18.3)	50 (14.79)
Treatment-related	24 (7.1)	18 (5.3)
Adverse event leading to treatment discontinuation	44 (13.0)	30 (8.8)
Treatment-related	36 (10.6)	22 (6.6)
Adverse event leading to dose adjustment/interruption	233 (68.7)	205 (60.5)
Treatment-related	214 (63.1)	192 (56.6)
Adverse events requiring additional therapy	248 (73.2)	96 (28.3)
Treatment-related	149 (44.0)	59 (17.4)
Adverse events by preferred term in ≥ 10% of patients		
Neutropenia	239 (70.5)	176 (51.9)
Treatment-related	234 (69.0)	175 (51.6)
Nausea	81 (23.9)	1 (0.3)
Treatment-related	71 (20.9)	1 (0.3)
Leucopenia	88 (26.0)	26 (7.7)
Treatment-related	86 (25.4)	26 (7.7)
Fatigue	65 (19.2)	9 (2.7)
Treatment-related	53 (15.6)	5 (1.5)
Anemia	61 (18.0)	12 (3.5)
Treatment-related	53 (15.6)	6 (1.8)
Alanine aminotransferase increase	54 (15.9)	21 (6.2)
Treatment-related	45 (13.3)	18 (5.3)
Alopecia	49 (14.5)	0 (0)
Treatment-related	39 (11.5)	0 (0)
Vomiting	46 (13.6)	3 (0.9)
Treatment-related	32 (9.4)	2 (0.6)
Aspartate aminotransferase increase	45 (13.3)	11 (3.2)
Treatment-related	37 (10.9)	7 (2.1)
Back pain	45 (13.3)	3 (0.9)
Diarrhea	39 (11.5)	2 (0.6)
Treatment-related	21 (6.2)	1 (0.3)
Headache	39 (11.5)	1 (0.3)
Arthralgia	36 (10.6)	2 (0.6)
Treatment-related	23 (6.8)	2 (0.6)
Pruritis	36 (10.6)	2 (0.6)
Treatment-related	30 (8.8)	2 (0.6)
Rash	34 (10.0)	2 (0.6)
Treatment-related	21 (6.2)	2 (0.6)

Transaminase elevations were the most common hepatobiliary AEs; treatment-related elevations of alanine aminotransferase considered serious occurred in 2 patients and led to hospitalization in 1 patient. The necessity for treatment withdrawal, dose reduction, or drug interruption related to hepatobiliary toxicity was necessary for less than 6% of patients, and aminotransferase increases recovered or resolved over time in most patients.

Myelosuppression primarily consisted of neutropenia, which occurred in 239 patients (70.5%; any grade) and was considered to be treatment-related in 228 patients (67.3%); neutropenia resolved over time in most patients. There were 3 occurrences of febrile neutropenia (0.9%) leading to hospitalization.

Eighteen patients (5.3%) had QTc prolongation (treatment-related in 17 patients), and 2 patients (0.6%) had syncope (treatment-related in 1 patients). QTc prolongation grade ≥ 3 occurred in just 3 patients (0.9%). In the majority of patients, it was not required to reduce the drug dose, interrupt or withdraw treatment, or administer additional therapy, and the QTc prolongation resolved over time. There were no cases of hepatobiliary toxicity, myelosuppression, or QTc prolongation leading to death.

Efficacy

A total of 3,246 patients were evaluated in the overall CompLEEment-1 study over a median follow-up duration of 25.4 months and a median duration of exposure to ribociclib of 17.5 months (range, 0.0–33 months).[26] The median TTP was 27.1 months, and the ORR was 43.6% (95% CI 41.5–45.8%). The CBR (was 69.1% (95% CI 67.1–71.1%) for patients with measurable disease at baseline.[28] Median PFS was 26.7 months (95% CI 24.8–30.1%).

In the SERCE population, 230 patients (67.8%) had measurable disease at baseline, and 109 (32.2%) non-measurable disease only. Efficacy analysis of the whole SERCE subgroup (N = 339) showed an ORR of 27.4% (Table 4). The CBR was 74.6%, and the median TTP was 24.4 months. In patients with measurable disease at baseline, the ORR% was 39.6% (Table 4), with a CBR of 73.9%.

Discussion

The CompLEEment-1 trial in a large, diverse patient cohort is the largest phase 3 clinical trial to date to evaluate the safety and efficacy of a CDK4/6

inhibitor, as well as one of the largest trials ever conducted in the advanced breast cancer setting. The use of cytotoxic chemotherapy in the first-line treatment of HR+/HER2− advanced breast cancer is still a frequent choice for many clinicians, despite the fact that most international recommendations recommend it only in the event of a visceral crisis. Therefore, results with the use of a CDK4/6 inhibitor in combination with endocrine therapy from studies such as CompLEEment-1 may help change therapy approaches for this patient population, delaying the need for chemotherapy.

This subgroup analysis of the SERCE patient population confirmed the safety and tolerability of ribociclib in combination with letrozole in patients with HR+/HER2− advanced breast cancer who have not previously received endocrine therapy for advanced disease and supports the interim efficacy data analysis of the overall CompLEEment-1 study population.

Patient populations in the SERCE subgroup were very similar to those in the overall CompLEEment-1 population. In general, efficacy data and safety data were similar. Of interest, any AEs, AEs ≥ grade 3, and treatment-related AEs, AEs leading to discontinuation or dose adjustment/interruption were slightly lower in the SERCE population. However, no reliable conclusions can be drawn for this finding.

The safety results are consistent with those observed in the pivotal MONALEESA-2[17,19] and MONALEESA-7[21] clinical trials, despite the less restrictive inclusion and exclusion criteria of CompLEEment-1, and no new safety signals were observed.

The CompLEEment-1 and MONALEESA-2 and MONALEESA-7 studies had very similar patient populations overall, with no significant differences between the SERCE population of CompLEEment-1 and patients in MONALEESA-2 and MONALEESA-7, with the exception of a higher number of metastatic sites at baseline in the SERCE patients (≥ 3 in 38.7% *vs*. 34.1% and 35.3%, respectively), and the enrolment of men (1.2 %) and patients with performance status 2 (3,5%), 28.7% women in SERCE population of CompLEEment-1 were premenopausal (MONALEESA-7 enrolled premenopausal women, MONALEESA-2 enrolled postmenopausal women only). Also, as expected, patients in MONALEESA-2 tended to be slightly older than those in the SERCE population of CompLEEment-1 (median age 62 *vs*. 58 years; age ≥ 65 years, 38.7% *vs*. 32.7%).

Analysis of the safety results comparing the two trials highlighted that the rate of side effects was similar, if somewhat higher in the MONALEESA-2 trial. For example, in MONALEESA-2, 98.5% (*vs*. 97.9%) had an AE, which was ≥ grade 3 in 70.7% versus 70.2%, and rates of neutropenia, leucopenia, and elevated levels of alanine aminotransferase and aspartate aminotransferase were higher in MONALEESA-2. Correspondingly, in MONALEESA-7, 98.2% of patients had an AE, which were grade ≥ 3 in 76.7%, and rates of grade ≥ 3 neutropenia and leucopenia were also higher than in CompLEEment-1. Hepatobiliary toxicity, an AE of special interest for the study, was lower in the SERCE population, although more medications were taken than in MONALEESA-2. However, the significance of this is unclear.

The reversible myelosuppression associated with ribociclib in CompLEEment-1 and the MONALEESA trials reflects on-target CDK4/6 inhibition, and the elevation in aminotransferase levels, which were largely reversible with dose adjustment, have also been observed with other CDK4/6 inhibitors in combination with aromatase inhibitors.[15,27,28] Ribociclib-related QTc prolongation occurred in 5% of patients and was generally manageable without the requirement to reduce the drug dose, interrupt or withdraw treatment, or administer additional therapy. Careful monitoring to detect AEs in a timely manner to limit the incidence of these events should be implemented when these agents are used in routine clinical practice.

Neutropenia, hepatobiliary toxicity, transaminase elevations, and QTc prolongation are AEs of special interest with ribociclib. Although the number of events leading to treatment discontinuation was low in our patients, the results of a study ex-

TABLE 4. Best overall response according to local assessment for patients in the SERCE subgroup of CompLEEment-1

No. (%)	All patients (*N* = 339)	Patients with measurable disease at baseline (*N* = 230)
Complete response	2 (0.6)	0 (0)
Partial response	91 (26.8)	91 (39.6)
Non-CR / Non-PD	90 (26.5)	–
Stable disease	108 (31.9)	106 (46.1)
Progressive disease	14 (4.1)	11 (4.8)
Unknown	34 (10.0)	22 (9.6)
Overall response rate (CR + PR)	93 (27.4)	91 (39.6)
Clinical benefit rate[a]	253 (74.6)	170 (73.9)

CR = complete response; PD = progression disease; PR = partial response;
[a]CR + PR + stable disease /non-progressive disease ≥ 24 months

ploring whether a reduced dosing regimen of 400 mg ribociclib 3-weeks on/1-week-off may decrease the risk of AEs of special interest (ClinicalTrials.gov Identifier NCT03822468) without compromising efficacy are awaited. However, OS (which was investigated in the pivotal MONALEESA trials with ribociclib at the 600 mg dose) is not an endpoint in the study.

As noted, the CompLEEment-1 and the MONALEESA-2 and MONALEESA-7 studies had very similar patient populations, and it is of interest to compare the efficacy findings. In analyses of patients with measurable disease at baseline, the ORR was 43.6% and the CBR 69.1% in the overall CompLEEment-1 patient population and 39.6% and 73.9%, respectively, in the SERCE population, compared with 40.7% and 79.6%, respectively, in the ribociclib group of MONALEESA-2[17] and 50.9% and 79.9%, respectively, in MONALEESA-7[21], suggesting similar efficacy overall and in the SERCE subgroup.

Overall, our analysis has confirmed the safety of the drug combination and showed promising data on efficacy, with dose interruptions not higher in the CompLEEment-1 trial compared to MONALEESA-2.

The CompLEEment-1 study has a number of strengths, including the large number of patients enrolled, the broad inclusion criteria that allowed the enrolments of pre-menopausal women and males, and permitted the receipt of chemotherapy prior to CDK therapy and an ECOG performance status of 2, resulting in a study population closer to real-world clinical practice. Mature data from the full patient population of the CompLEEment-1 trial will provide further valuable information on the role of ribociclib plus letrozole in patients with HR+/HER2− advanced breast cancer.

The study also has some limitations. The median follow-up duration is as yet relatively short, limiting the number of events recorded, including disease progression and death. Of note, patients in CompLEEment-1 were followed up to the point of discontinuing ribociclib, for whatever reason, and therefore the progression follow-up is more conservative than in the pivotal trials, where patients discontinuing ribociclib for toxicity but remaining on endocrine therapy remain within the study.

Finally, the SERCE population represents only a small proportion of the full CompLEEment-1 cohort.

Of interest for future analysis when data are available are the contribution of ribociclib to health-related quality of life (HR-QoL) in our patients and the influence of concomitant medications or therapy on outcome and the incidence of side effects. Patient-reported outcomes are not yet available for CompLEEment-1. However, data from MONALEESA-2 shows that HR-QoL was consistently maintained, and in MONALEESA 7 was significantly improved from baseline in patients receiving ribociclib plus letrozole, compared to the placebo arm.[21,29]

Similarly, the impact of health status (e.g., comorbidities), AEs, and/or dose interruptions or reduction on QoL will be analyzed as data become available.

Conclusions

These findings from a subgroup of the large CompLEEment-1 trial support the safety and manageable tolerability profile of ribociclib in a broad range of patients with HR+/HER2-advanced breast cancer more representative of patients in real-world clinical practice than those enrolled in the pivotal clinical trials.

Acknowledgments

The authors thank the patients who participated in the study and their families, staff members at each study site, and Katarina Petrakova for helpful discussion and critical comments. Medical writing assistance was provided by Ray Hill, an independent medical writer, on behalf of Springer Healthcare. This was funded by Novartis Pharmaceuticals.

The CompLEEment-1 trial was sponsored by Novartis Pharmaceuticals.

Contributors and data availability

All authors contributed to the conception or design of this analysis. All authors were involved in data interpretation; writing or reviewing and editing the manuscript; and approved the final version for submission. Data collection and analysis were completed by trial sponsor representatives. The corresponding authors had final responsibility for the decision to submit for publication.

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.novartisclini-

caltrials.com/TrialConnectWeb/home.nov). Data are however available from the authors upon reasonable request and with permission of Novartis Pharmaceuticals Corporation.

Study locations for the CompLEEment-1 trial as well as SERCE study investigators and sub-investigators for the CompLEEment-1 trial are listed in Supplementary file 1.

References

1. Ferlay J, Colombet M, Soerjomataram I, Mathers C, Parkin DM, Pineros M, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. *Int J Cancer* 2019; **144:** 1941-53. doi: 10.1002/ijc.31937
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; **68:** 394-424. doi: 10.3322/caac.21492
3. Yousef AJA. Male breast cancer: epidemiology and risk factors. *Semin Oncol* 2017; **44:**. 267-72. doi: 10.1053/j.seminoncol.2017.11.002
4. Turashvili G, Brogi E. Tumor heterogeneity in breast cancer. *Front Med* 2017; **4:** 227. doi: 10.3389/ fmed.2017.00227
5. Howlader N, Cronin KA, Kurian AW, Andridge R. Differences in breast cancer survival by molecular subtypes in the United States. *Cancer Epidemiol Biomarkers Prev* 2018; **27:** 619-26. doi: 10.1158/1055-9965.EPI-17-0627
6. National Institute for Health and Care Excellence (NICE). Advanced breast cancer: diagnosis and treatment CG81. Updated 2017. [Internet]. [cited 2022 Jan 15]. Available at: https://www.nice.org.uk/guidance/cg81
7. Cardoso F, Paluch-Shimon S, Senkus E, Curigliano G, Aapro MS, Andre F, et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). *Ann Oncol* 2020; **31:** 1623-49. doi: 10.1016/j.annonc.2020.09.010
8. Gradishar WJ, Anderson BO, Balassanian R, Blair SL, Burstein HJ, Cyr A, et al. Breast cancer, version 4.2017, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 2018; **16:** 310-20. doi: 10.6004/jnccn.2018.0012
9. Telli ML, Gradishar WJ, Ward JH. NCCN Guidelines updates: breast cancer. *J Natl Compr Canc Netw* 2019; **17:** 552-5. doi: 10.6004/jnccn.2019.5006
10. Robertson JFR, Bondarenko IM, Trishkina E, Dvorkin M, Panasci L, Manikhas A et al. Fulvestrant 500 mg versus anastrozole 1 mg for hormone receptor-positive advanced breast cancer (FALCON): an international, randomised, double-blind, phase 3 trial. *Lancet* 2016; **388**: 2997-3005. doi: 10.1016/S0140-6736(16)32389-3
11. Yamamoto-Ibusuki M, Arnedos M, Andre F. Targeted therapies for ER+/HER2- metastatic breast cancer. *BMC Med* 2015; **13:** 137. doi: 10.1186/s12916-015-0369-5
12. Araki K, Miyoshi Y. Mechanism of resistance to endocrine therapy in breast cancer: the important role of PI3K/Akt/mTOR in estrogen receptor-positive, HER2-negative breast cancer. *Breast Cancer* 2018; **25:** 392-401. doi: 10.1007/s12282-017-0812-x
13. AlFakeeh A, Brezden-Masley C. Overcoming endocrine resistance in hormone receptor-positive breast cancer. *Curr Oncol* 2018; **25(Suppl 1):** S18-27. doi: 10.3747/co.25.3752
14. Hamilton E, Infante JR. Targeting CDK4/6 in patients with cancer. *Cancer Treat Rev* 2016; **45:** 129-38. doi: 10.1016/j.ctrv.2016.03.002
15. 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:** 1925-36. doi: 10.1056/NEJMoa1607303
16. Sledge GW Jr, Toi M, Neven P, Sohn J, Inoue K, Pivot X, 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:** 2875-84. doi: 10.1200/JCO.2017.73.7585
17. Hortobagyi GN, Stemmer SM, Burris HA, Yap YS, Sonke GS, Paluch-Shimon S, et al. Ribociclib as first-line therapy for HR-positive, advanced breast cancer. *N Engl J Med* 2016; **375:** 1738-48. doi: 10.1056/NEJMoa1609709
18. Tripathy D, Bardia A, Sellers WR. Ribociclib (LEE011): mechanism of action and clinical impact of this selective cyclin-dependent kinase 4/6 inhibitor in various solid tumors. *Clin Cancer Res* 2017; **23:** 3251-62. doi:10.1158/1078-0432.Ccr-16-3157
19. 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:** 1541-7. doi: 10.1093/annonc/mdy155
20. Slamon DJ, Neven P, Chia S, Fasching PA, De Laurentiis M, Im SA, et al. Phase III randomized study of ribociclib and fulvestrant in hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: MONALEESA-3. *J Clin Oncol* 2018; **36:** 2465-72. doi: 10.1200/JCO.2018.78.9909
21. 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:** 904-15. doi: 10.1016/S1470-2045(18)30292-4
22. 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:** 942-50. doi: 10.1056/NEJMoa2114663
23. Tripathy D, Im S, Colleoni M, Franke F, Bardia A, Harbeck N, et al. Updated overall survival (OS) results from the phase III MONALEESA-7 trial of pre- or perimenopausal patients with hormone receptor positive epidermal growth factor receptor 2 negative (HR+/HER2–) advanced breast cancer (ABC) treated with endocrine therapy (ET) ± ribociclib. [Abstract PD2-04]. San Antonio Breast Cancer Virtual Symposium, San Antonio, Texas, USA, December 8-12, 2020. doi: 10.1158/1538-7445.SABCS20-PD2-04
24. Slamon DJ, Neven P, Chia S, Fasching PA, De Laurentiis M, Im SA, et al. Overall survival with ribociclib plus fulvestrant in advanced breast cancer. *N Engl J Med* 2020; **382:** 514-24. doi: 10.1056/NEJMoa1911149
25. DeLaurentiis M, Neven P, Jerusalem GHM, Bachelot TD, Jacot W, Dent SF, et al. Ribociclib (RIBO) + letrozole (LET) in patients (pts) with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2–) advanced breast cancer (ABC) with no prior endocrine therapy (ET) for ABC: Preliminary results from the phase 3b CompLEEment-1 trial. [Abstract 1056P]. *J Clin Oncol* 2018; **36:** 1056. doi: 10.1200/JCO.2018.36.15_suppl.1056
26. 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 Res Treat* 2021; **189:** 689-99. doi: 10.1007/s10549-021-06334-0
27. Bilgin B, Sendur MAN, Sener Dede D, Akinci MB, Yalcin B. A current and comprehensive review of cyclin-dependent kinase inhibitors for the treatment of metastatic breast cancer. *Curr Med Res Opin* 2017; **33:** 1559-69. doi: 10.1080/03007995.2017.1348344
28. Finn RS, Aleshin A, Slamon DJ. Targeting the cyclin-dependent kinases (CDK) 4/6 in estrogen receptor-positive breast cancers. *Breast Cancer Res* 2016; **18:** 17. doi: 10.1186/s13058-015-0661-5
29. Verma S, O'Shaughnessy J, Burris HA, Campone M, Alba E, Chandiwana 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:** 535-45. doi:10.1007/s10549-018-4769-z