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CLINICAL TRIAL

Ribociclib plus letrozole in male patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: subgroup analysis of the phase IIIb CompLEEment-1 trial

Mario Campone[1] · Michelino De Laurentiis[2] · Claudio Zamagni[3] · Igor Kudryavcev[4] · Mariëtte Agterof[5] · Ursa Brown-Glaberman[6] · Markéta Palácová[7] · Sanjoy Chatterjee[8] · Lakshmi Menon-Singh[9] · Jiwen Wu[9] · Miguel Martín[10]

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Abstract

Purpose CompLEEment-1 (NCT02941926) is a single-arm, open-label, multicentre phase IIIb study investigating the safety and efficacy of ribociclib plus letrozole (RIB + LET) in a large, diverse cohort who have not received prior endocrine therapy (ET) for advanced disease. We present an exploratory analysis of male patients.

Methods Eligible patients with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2−) advanced breast cancer (ABC), who had no prior ET and ≤ 1 line of prior chemotherapy for advanced disease, received RIB + LET. Male patients also received goserelin or leuprolide. Primary endpoint was safety and tolerability; efficacy was a secondary endpoint.

Results In total, 39/3246 patients were male. Baseline characteristics were similar to the overall population. Male patients experienced fewer treatment-related adverse events (AEs) and treatment-related serious AEs compared with the overall population; fewer male patients had treatment-related AEs leading to discontinuation, adjustment/interruption, or additional therapy. One male patient died as a result of a serious AE that was not considered to be treatment-related. The most common AE was neutropenia; the incidence of grade ≥ 3 neutropenia in males (41.0%) was lower than in the overall population (57.2%). Median follow-up was 25.4 months; median time to progression was not reached in males versus 27.1 months for the overall population.

Conclusion The clinical benefit and overall response rates in males were consistent with the overall population. This analysis demonstrates the safety and efficacy of ribociclib in a close-to-real-world setting, supporting the use of RIB + LET in male patients with HR+, HER2− ABC.

Trial registration number: NCT02941926 (Registered 2016).

Keywords Advanced breast cancer · Ribociclib · Men · Real-world evidence · Male breast cancer

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✉ Mario Campone
mario.campone@ico.unicancer.fr

1 Western Cancer Institute, Nantes, France

2 Istituto Nazionale Tumori IRCCS "Fondazione Pascale", Naples, Italy

3 IRCCS Azienda Ospedaliero-Universitaria Di Bologna, Bologna, Italy

4 Kaluga Regional Clinical Oncology Center, Kaluga, Russian Federation

5 St. Antonius Hospital, Utrecht/Nieuwegein, The Netherlands

6 University of New Mexico Cancer Center, Albuquerque, NM, USA

7 Masaryk Memorial Cancer Institute, Brno, Czech Republic

8 Tata Medical Center, Kolkata, India

9 Novartis Pharmaceuticals, East Hanover, NJ, USA

10 Gregorio Marañón General University Hospital, Madrid, Spain

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Introduction

The incidence of breast cancer in males is up to 100-fold less than in females [1]. However, the percentage increase in the incidence of breast cancer between 1990 and 2017 is higher in males than in females [2]. In 2020, it was estimated that 2620 males in the USA would be diagnosed with invasive breast cancer and 520 would die from this disease. Furthermore, it is now anticipated that more males will die from breast cancer than testicular cancer in the USA [3–5]. Recent guidance issued by the US Food and Drug Administration (FDA) includes recommendations for the inclusion of males in clinical trials of breast cancer drugs [6]. However, historically, male patients were rarely included in breast cancer clinical trials, and treatment guidelines for this population are often proposed based on data from female patients [1].

As in females, most cases of breast cancer in males are defined immunohistochemically as hormone receptor-positive (HR+) [7–9]. For many years, endocrine therapy (ET) has been the treatment of choice for patients with HR+ advanced breast cancer (ABC), and there is a trend for a statistically significant increase in the reported proportion of males with breast cancer receiving ET [9, 10]. In males, ET is recommended preferably with a luteinising hormone-releasing hormone agonist (LHRH) [11]. Aromatase inhibitors increase the levels of testosterone and other hormones, thereby providing excess substrate that subsequently counteracts the aromatase inhibitor-mediated block [12]. LHRH agonists can inhibit the hypothalamic–pituitary feedback loop and reduce the substrate for aromatization. A common feature of breast cancer in both males and females is resistance to ET therapy (either intrinsic at baseline or acquired after exposure to treatment), which is a barrier to long-term clinical benefit and necessitates the development of therapies that reverse or delay this resistance [13].

Administration of targeted therapy in combination with ET has been shown to provide a clinically meaningful delay in the development of endocrine resistance [14]. Ribociclib is an oral, selective, cyclin-dependent kinases 4 and 6 inhibitor (CDK4/6i) approved for use in combination with ET for the treatment of females with HR+, human epidermal growth factor receptor 2-negative (HER2−) ABC [15, 16]. The MONALEESA trial programme has assessed ribociclib in multiple phase III clinical trials. In patients with HR+, HER2− ABC, superior clinical benefit has been consistently demonstrated with ribociclib + ET compared with ET alone, including statistically significant improved overall survival (OS) in both premenopausal females (in combination with a nonsteroidal aromatase inhibitor, MONALEESA-7 [NCT02278120] [17, 18]) and in postmenopausal females (in combination with fulvestrant, MONALEESA-3 [NCT02422615] [19, 20] and in combination with letrozole, MONALEESA-2 [NCT01958021]) [21, 22]. Of note, males with HR+, HER2− ABC were eligible to enrol in MONALEESA-3; no male patient enrolled in this study [20].

The CompLEEment-1 trial (NCT02941926) is a single-arm, open-label, multicentre phase IIIb study investigating the safety and efficacy of ribociclib in combination with letrozole in a large, diverse patient cohort, including male patients, which is representative of real-world clinical practice, who have not received prior ET for advanced disease. The trial included a Core Phase (time from the first patient's first visit to 18 months after last patient/first visit) and a follow-on Extension Phase to the last patient's last visit [23]. Here, we report safety and efficacy results for the male subgroup from the Core Phase.

Methods

Study design and treatment

CompLEEment-1 is a multicentre phase IIIb clinical trial designed to evaluate the safety, tolerability, and efficacy of ribociclib in combination with letrozole in males and pre-/postmenopausal females with HR+, HER2− ABC and no prior ET for advanced disease (Fig. 1); detailed methods have been reported previously [23]. Briefly, eligible patients with HR+, HER2− ABC who had no prior ET and up to one line of prior chemotherapy for advanced disease were treated with ribociclib (600 mg) plus letrozole (2.5 mg) with or without food. Males and pre-/perimenopausal females also received concomitant luteinising hormone-releasing hormone agonist goserelin (3.6 mg) or leuprolide (7.5 mg).

Eligibility

Key inclusion criteria included the following: locally advanced or metastatic HR+, HER2− breast cancer not amenable to curative therapy; no prior ET for advanced disease; Eastern Cooperative Oncology Group performance status (ECOG PS) of ≤ 2; ≤ 1 line of chemotherapy for advanced disease; disease-free interval > 12 months from completion of (neo)adjuvant therapy if treatment included a nonsteroidal aromatase inhibitor; adequate bone marrow and organ function; and QT interval corrected by Fridericia's formula (QTcF) of < 450 ms and resting heart rate of ≥ 50 bpm at screening electrocardiogram. Key exclusion criteria included prior treatment with a CDK4/6i and/or systemic hormonal therapy for ABC; concurrent malignancy ≤ 3 years prior to starting study drug (except adequately treated basal cell or squamous cell

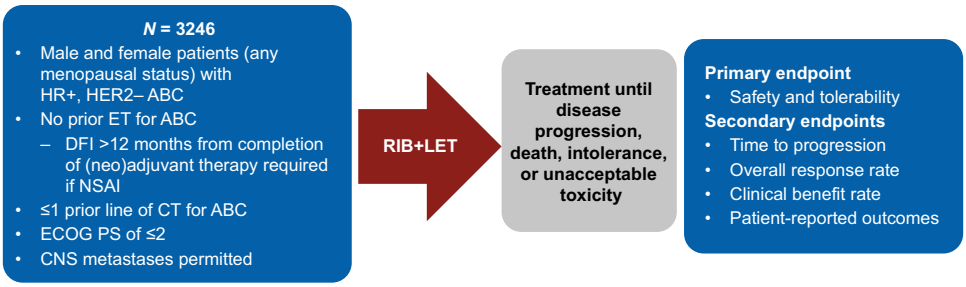

Fig. 1 CompLEEment-1 trial design. Patients were followed for 30 days after premature discontinuation of ribociclib or after treatment completion, as per protocol. *ABC* advanced breast cancer, *CNS* central nervous system, *CT* chemotherapy, *DFI* disease-free interval, *ECOG PS* Eastern Cooperative Oncology Group performance status, *ET* endocrine therapy, *HER2*− human epidermal growth factor receptor 2-negative, *HR*+ hormone receptor-positive, *LET* letrozole, *NSAI* nonsteroidal aromatase inhibitor, *RIB* ribociclib

carcinoma, non-melanomatous skin cancer or curatively resected cervical cancer); central nervous system metastases (unless lesions are clinically stable for ≥ 4 weeks); clinically significant heart disease and/or recent cardiac events (e.g. uncontrolled hypertension); and a gastrointestinal impairment or disease that may significantly alter study drug absorption.

Endpoints

The primary endpoint was safety/tolerability. This was measured by the number of patients who experienced adverse events ([AEs] any AEs; grade 3/4 AEs; serious AEs [SAEs]; AEs of special interest [AESIs]) as well as AEs leading to dose reduction, interruption, or AE-related deaths and discontinuation. AESIs comprised neutropenia, QTcF prolongation, and hepatobiliary toxicity. An exploratory analysis assessed exposure-adjusted AEs.

Key secondary endpoints were time to progression (TTP) based on investigator assessment, overall response rate (ORR) for patients with measurable disease, and clinical benefit rate (CBR).

Assessments

Safety was monitored by assessing patient symptoms through physical exams and assessing biochemical and haematologic laboratory values at various time points during the Core Phase. AEs were characterised and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), v4.03 [24]. Tumour response was assessed locally based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Tumour assessments were performed according to the current standard of care, with assessments recommended to take place at least every 12 weeks until disease progression.

Statistical analysis

The safety and efficacy analyses were based on patients who received ≥ 1 dose of either ribociclib or letrozole or goserelin/leuprolide (if applicable) in the Core Phase. The primary endpoint of safety/tolerability was summarised descriptively in the safety analysis set. For the secondary efficacy endpoints, distribution was estimated using the Kaplan–Meier method and descriptive statistics.

Results

Patient characteristics and disposition

Of the 3246 patients who were enrolled and received ≥ 1 dose of study treatment between 30 November 2016 and 22 March 2018, 39 were male. Baseline characteristics for these patients are shown in Table 1. The majority of males ($n = 28$; 71.8%) were White. The median age of the male subgroup was 62.0 years and 15 (38.5%) were aged ≥ 65 years. More than one quarter of male patients ($n = 12$; 30.8%) had four or more metastatic sites, and the most common sites of metastasis were bone (69.2%), lung (61.5%), and lymph nodes (33.3%). About half of male patients received prior chemotherapy ($n = 21$; 53.8%, in the metastatic [$n = 2$; 5.1%], adjuvant [$n = 18$; 46.2%], and neoadjuvant [$n = 3$; 7.7%], settings), and prior adjuvant ET ($n = 20$, 51.3%). The cut-off date for this analysis was 8 November 2019. At data cut-off, 21/39 male patients (53.8%) had completed treatment in the Core Phase, with 16/39 (41.0%) entering the Extension Phase. The median duration of exposure to ribociclib in this population was 19.2 months (versus 17.5 months in the overall population), and the median duration of exposure to letrozole was 19.4 months (versus 17.7 months in the overall population). In total, 18/39 (46.2%) male patients permanently discontinued treatment compared with 1945/3246 (59.9%) in the overall population. The most cited reasons

Table 1 Patient characteristics at baseline

Characteristic	All patients ($N=3246$)	Male patients ($N=39$)
Median age, years (range)	58.0 (20–92)	62.0 (33–80)
Age ≥ 65 years, *n* (%)	1073 (33.1)	15 (38.5)
Patient race, *n* (%)		
Caucasian	2553 (78.7)	28 (71.8)
Asian	227 (7.0)	3 (7.7)
Black	29 (0.9)	1 (2.6)
Native American	18 (0.6)	0
Pacific Islander	1 (0.03)	0
Other/unknown	418 (12.9)	7 (17.9)
ECOG PS 1–2, *n* (%)	1273 (39.2)	18 (46.2)
Histological grade, *n* (%)		
Well differentiated	297 (9.1)	4 (10.3)
Moderately differentiated	1306 (40.2)	12 (30.8)
Poorly differentiated	626 (19.3)	13 (33.3)
Undifferentiated	30 (0.9)	0
Unknown	987 (30.4)	10 (25.6)
Metastatic sites, *n* (%)		
0	15 (0.5)	0
1	903 (27.8)	11 (28.2)
2	923 (28.4)	11 (28.2)
3	644 (19.8)	5 (12.8)
4	375 (11.6)	11 (28.2)
≥ 5	386 (11.9)	1 (2.6)
Current extent of disease (metastatic sites), *n* %		
Bone	2409 (74.2)	27 (69.2)
Bone only	704 (21.7)	7 (17.9)
Breast	183 (5.6)	0
CNS	51 (1.6)	0
Visceral	1992 (61.4)	27 (69.2)
Liver	862 (26.6)	8 (20.5)
Lung	1416 (43.6)	24 (61.5)
Other	295 (9.1)	2 (5.1)
Skin	110 (3.4)	2 (5.1)
Lymph nodes	1250 (38.5)	13 (33.3)
Others	163 (5.0)	2 (5.1)

ECOG PS Eastern Cooperative Oncology Group performance status

for treatment discontinuation in the male population were progressive disease (28.2%) and AEs (10.3%); these were similar to the proportions reported for the overall population (progressive disease, 34.2% and AEs, 15.5%).

Safety

Safety was evaluated in all 39 male patients and an overview of AEs is summarised in Table 2. Male patients experienced fewer treatment-related AEs and treatment-related SAEs (both all grade and grade ≥ 3) compared with the overall population. In addition, fewer male patients had treatment-related AEs (all grade and grade ≥ 3) that led to discontinuation, adjustment/interruption, or additional therapy. The mean relative dose intensity (RDI) for males receiving ribociclib was 91.3% (median 98.6%), with an average daily dose of 570.4 mg (median 600.0 mg). This was similar to the overall population, with a mean RDI for ribociclib of 86.4% (median 95.2%) and an average daily dose of 547.7 mg (median 600.0 mg). Generally, fewer males experienced AEs that required additional therapy compared with the overall population, and no treatment-related fatal AEs were observed in male patients.

The most common all-grade AEs were neutropenia (53.8%), hot flush (33.3%), and diarrhoea (25.6%); the most common grade ≥ 3 AE was neutropenia (41.0%). With regards to AESIs, the incidence of neutropenia was generally lower in the male population compared with the overall population (Table 3). Increases in alanine aminotransferase and aspartate aminotransferase observed in male patients were similar to those in the overall population, whilst the incidences of all grade and grade ≥ 3 QT interval prolongation were higher in male patients but without apparent clinical impact.

Most male patients ($n=33$; 84.6%) required a ribociclib dose interruption; the most common reason for this was an AE (74.4% of male patients). However, the majority of male patients ($n=32$; 82.1%) did not require a ribociclib dose reduction; of those that did, the most common reason was an AE (17.9% of male patients). These findings were broadly similar to those in the overall population, in which 86.8% of patients had a ribociclib dose interruption (76.2% of patients had a dose interruption due to an AE) and 61.3% did not require a ribociclib dose reduction. Few male patients (10.3%) permanently discontinued due to an AE. The most common AEs that led to either dose interruption or reduction in male patients were neutropenia (25.6% and 7.7%, respectively) and decreased neutrophil count (12.8% and 2.6%, respectively).

Efficacy

The median duration between tumour assessments was 12 weeks (mean: 13 weeks), which shows that the frequency of tumour assessments was conducted according to protocol (every 12 weeks). TTP results are summarised in Fig. 2. Over a median follow-up of 25.4 months for the overall population, the median TTP was 27.1 months (95% confidence interval [CI] 25.7–not reached [NR]), and for male patients the median TTP was NR (95% CI 16.8–NR). After 30 months, the estimated event-free probability for males was 61.4% (95% CI 38.4–77.9).

Table 2 Overview of adverse events

Category, *n* (%)	All patients (*N* = 3246)		Male patients (*N* = 39)	
	All grades	Grade ≥ 3	All grades	Grade ≥ 3
AEs	3203 (98.7)	2461 (75.8)	38 (97.4)	26 (66.7)
Treatment-related	3091 (95.2)	2192 (67.5)	36 (92.3)	21 (53.8)
SAEs	702 (21.6)	590 (18.2)	6 (15.4)	5 (12.8)
Treatment-related	203 (6.3)	178 (5.5)	1 (2.6)	1 (2.6)
Fatal SAEs	62 (1.9)	61 (1.9)	1 (2.6)	1 (2.6)
Treatment-related	14 (0.4)	14 (0.4)	0	0
AEs leading to discontinuation	528 (16.3)	310 (9.6)	4 (10.3)	2 (5.1)
Treatment-related	418 (12.9)	237 (7.3)	3 (7.7)	2 (5.1)
AEs leading to dose adjustment/interruption	2434 (75.0)	2095 (64.5)	28 (71.8)	22 (56.4)
Treatment-related	2235 (68.9)	1964 (60.5)	23 (59.0)	19 (48.7)
AEs requiring additional therapy	2624 (80.8)	844 (26.0)	30 (76.9)	8 (20.5)
Treatment-related	1613 (49.7)	392 (12.1)	14 (35.9)	4 (10.3)

A patient with multiple severity grades for an AE was only counted under the maximum grade

AE adverse event, *SAE* serious adverse event

Table 3 Adverse events of special interest

Category, *n* (%)	All patients (*N* = 3246)		Male patients (*N* = 39)	
	All grades	Grade ≥ 3	All grades	Grade ≥ 3
Neutropenia[a]	2417 (74.5)	1856 (57.2)	21 (53.8)	16 (41.0)
ALT increased	526 (16.2)	249 (7.7)	6 (15.4)	3 (7.7)
AST increased	459 (14.1)	184 (5.7)	5 (12.8)	1 (2.6)
QTcF interval prolongation	217 (6.7)	33 (1.0)	5 (12.8)	1 (2.6)

Numbers (*n*) represent counts of patients. A patient with multiple severity grades for an AE was only counted under the maximum grade

AE adverse event, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *QTcF* QT interval corrected by Fridericia's formula

[a]Includes 'neutropenia' and 'neutrophil count decreased'

Results for the best ORR and CBR in patients with measurable disease are summarised in Fig. 3. Overall, the ORR and CBR benefits observed in male patients were consistent with the total population. For patients with measurable disease at baseline, most patients experienced a clinical benefit (71.9%, 95% CI 53.3–86.3%), with an ORR of 46.9% (95% CI 29.1–65.3%). The CBR and ORR rates in all male patients show similar results (76.9% and 41.0%, respectively). The median duration of response in male patients with measurable disease at baseline ($n = 15$) was not estimable (range, 4.2–24.6 months). The same median duration of response (not estimable; range, 4.2–24.6 months) was also observed in other male patients with confirmed partial or complete response ($n = 16$).

Discussion

Although male breast cancer is uncommon, its incidence is rising significantly. In the USA, the estimated incidence of male breast cancer has increased from 1970 cases in 2010 to 2620 cases in 2020, resulting in an estimated 390 and 520 deaths, respectively [5, 25]. Furthermore, males with breast cancer tend to present with their disease at an older age, with more comorbidities/other neoplasms (e.g. prostate cancer, colon cancer, lung cancer) and more advanced disease [26–28]. Breast cancer tumours in male patients also differ pathologically to those in women; for example, males are reported to have higher rates of HR+ breast cancer [27]. Emerging data are also revealing molecular

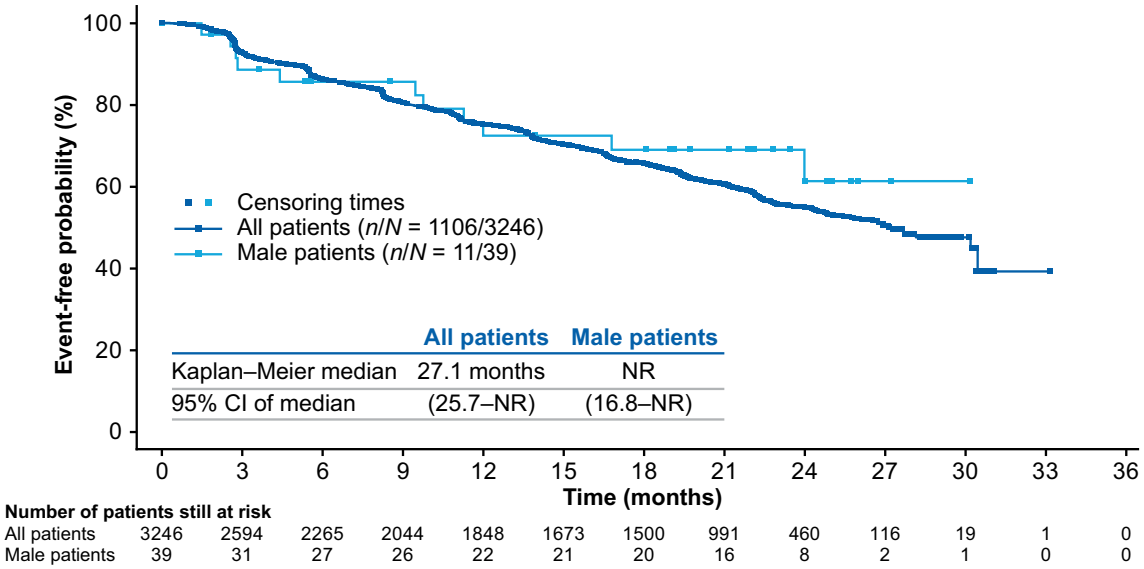

Fig. 2 Kaplan–Meier plot of time to progression. *CI* confidence interval, *NR* not reached

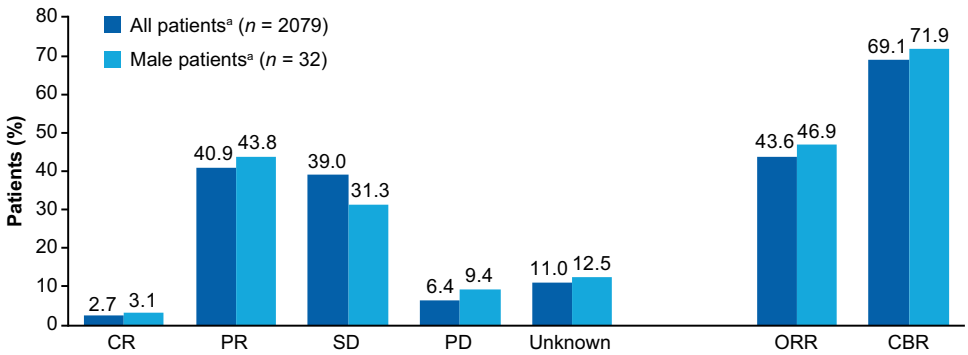

Fig. 3 Best overall response rate and clinical benefit rate for patients with measurable disease at baseline. [a]2079 out of 3246 patients (64.0%) in the overall population and 32 out of 39 (82.1%) male patients had measurable disease at baseline. *CBR* clinical benefit rate, *CR* complete response, *ORR* overall response rate, *PD* progressive disease, *PR* partial response, *SD* stable disease

differences between male and female breast cancer [29], but substantial knowledge gaps remain around the optimal management of breast cancer in male patients [30].

Compounding this issue is that fact that males have historically been excluded from clinical trials, because of the rarity of breast cancer in this population. The FDA has recently issued guidance that encourages the inclusion of male patients with breast cancer in clinical trials [6], but to date, there are no published data from prospective, randomised trials supporting a specific therapeutic approach in breast cancer in male patients [31]. This has led to limited FDA-approved treatment options in this setting [6], with treatment recommendations largely extrapolated from clinical trials in females [6, 30]. Current guidelines from the National Comprehensive Cancer Network state that breast cancer management in males is similar to management in females overall, although a lack of available data to support the use of some prognostic assays and treatments in male patients is noted [32]. Current American Society of Clinical Oncology (ASCO) guidelines recommend that males with HR+ breast cancer who are candidates for adjuvant chemotherapy should be offered tamoxifen for an initial 5 years. This recommendation is based on observational studies that have suggested an approximate 50% response rate [33], as well as a survival benefit, with the use of tamoxifen. The ASCO guidelines also recommend that males with metastatic HR+, HER2− breast cancer should be offered ET as first-line therapy (except in cases of visceral crisis or rapidly progressive disease) and that CDK4/6 inhibitors should be used in males as they are in females. Although data demonstrating the benefit and safety of CDK4/6 inhibitors in males are sparse, small case studies have been reported, and the FDA has granted approval for one CDK4/6i, palbociclib, in this setting [30]. However, this approval relied primarily on published data in females, due to the many limitations of the available data in male patients [34].

Improved OS has been consistently demonstrated with ribociclib compared with placebo in three pivotal phase

III studies (MONALEESA-3, MONALEESA-7, and MONALEESA-2 [17, 19, 22], as well as a consistent and manageable safety profile when investigated in combination with ET [18, 21, 35]. The CompLEEment-1 study has demonstrated the consistent safety and efficacy of ribociclib in combination with letrozole in male patients, similar to that observed in these previous pivotal phase III studies. Importantly, CompLEEment-1 has enrolled a much larger, more diverse cohort of patients with HR+, HER2− ABC who had not previously received ET for advanced disease [23], including those treated with prior chemotherapy for advanced disease, those with an ECOG PS of 2, those with stable CNS metastases, premenopausal females, and males—a population not well studied in randomised controlled trials [30].

The baseline characteristics of the male patients were largely in line with those reported for the overall population. The primary endpoint of this single-arm study was the safety and tolerability of ribociclib. The expected adverse reactions observed with ribociclib (neutropenia, QTcF prolongation, and hepatobiliary adverse reactions) can generally be effectively managed by following guidelines for dose interruption or reduction per the label and/or with medication [15, 16]. Consistent with previous phase III trials [17, 19, 35], the safety profile of ribociclib in combination with letrozole in male patients was manageable. Ribociclib was well tolerated, and male patients generally experienced fewer treatment-related AEs and SAEs (all grade and grade ≥ 3) compared with the overall population. Specifically, male patients experienced fewer events of neutropenia (all grade and grade ≥ 3) than the full population. Furthermore, the rate of permanent discontinuation from the study in male patients was low and even slightly lower than that of the overall population. Similarly, the proportion of male patients who experienced AEs requiring either dose adjustment/interruption or additional therapy was slightly lower when compared with the overall population. Indeed, coupled with the slightly higher mean RDI of ribociclib (91.3%) compared with the full population (86.4%), this suggests that ribociclib was generally very well tolerated; few male patients required a ribociclib dose modification and any interruptions to administration were not sustained.

The secondary endpoints were related to efficacy; a meaningful clinical benefit was demonstrated in this male subgroup (median TTP was not reached) compared with the overall population (median TTP 27.1 months). There were a relatively low number of patients in the male subgroup by 30 months; nonetheless, the event-free probability estimate at this timepoint was 61.4%. Moreover, the event-free probability data show consistency between the overall population and male patients. Similarly, the ORR and CBR rates of male patients showed concordance with the total population. Over 70% of male patients derived clinical benefit from ribociclib treatment and just under half had either partial or complete responses. This compares favourably with the response rate seen with tamoxifen treatment in male patients with breast cancer. Tamoxifen is considered a first-line option for male patients with metastatic breast cancer and has a reported response rate of approximately 50% [33]. Based on these data from male patients in the CompLEEment-1 trial, the FDA has recently approved an expanded indication of ribociclib + ET for male patients with HR+, HER2− advanced or metastatic breast cancer [15].

The limitations of this analysis include the exploratory (non-pre-specified) nature of the analysis, the absence of biomarker data, and that CompLEEment-1 is a single-arm trial that lacks a placebo control or other control arm. Although there are a relatively low number of male patients enrolled in the CompLEEment-1 trial, the proportion of male patients in relation to the overall trial population is reflective of the general clinical population. In addition, although it was recommended in the study protocol that response assessments were conducted at least every 12 weeks and the median interval duration was 12 weeks, the CompLEEment-1 trial design allows for different intervals according to the local standard of care, which may have introduced an element of bias into the data interpretation. Finally, the study duration does not allow evaluations of the longer-term impact of ribociclib treatment.

To conclude, results from this male subgroup analysis of patients from the CompLEEment-1 trial provide data on the largest cohort of male patients with breast cancer treated with a CDK4/6i in a clinical trial setting to date. These data demonstrate the safety and efficacy of ribociclib in male patients, which is consistent with the results seen in numerous phase III trials in females and supports the use of ribociclib in combination with letrozole in male patients with HR+, HER2− ABC [17, 19, 22, 35]. Where possible, male patients should be actively included in breast cancer clinical trials.

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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), which were used under licence

for the current study, and so are not publicly available. Data are, however, available from the authors upon reasonable request and with permission of Novartis Pharmaceuticals Corporation.

Code availability Not applicable.

Declarations

Conflict of interest Mario Campone received honoraria from GT1; honoraria to institution from Sanofi, Pierre Fabre, AstraZeneca, Servier, Novartis, AbbVie, Accord, and Pfizer; and advisory/consultancy fees from Sanofi, Pierre Fabre, AstraZeneca, Servier, Novartis, AbbVie, Accord, Pfizer, and GT1; and was a member of Speaker bureau for and received expert testimony fees from Novartis and Eli Lilly, outside the submitted work. Michelino De Laurentiis received speaker's honoraria and advisory board honoraria from Amgen, AstraZeneca, Celgene, Eisai, Eli Lilly, MSD, Novartis, Pfizer, and Roche, outside the submitted work. Claudio Zamagni received honoraria from Takeda, Pierre Fabre, Teva, and Instituto Gentili; consulting or advisory board fees from Roche, Eisai, Novartis, AstraZeneca, Pfizer, PharmaMar, Celgene, Eli Lilly, Amgen, Tesaro, and QuintilesIMS; research funding paid to institution from Roche/Genentech, Roche, AstraZeneca, Novartis, Medivation, AbbVie, Pfizer, Array BioPharma, Morphotek, Celgene, Tesaro, Synthon, and Seattle Genetics; and reimbursement of travel or accommodation expenses from Roche, Celgene, Novartis, Pierre Fabre, Instituto Gentili, Pfizer, Tesaro, and PharmaMar, outside the submitted work. Igor Kudryavcev has nothing to disclose. Mariëtte Agterof has nothing to disclose. Ursa Brown-Glaberman received advisory board honoraria from Novartis, Eisai, Seattle Genetics, and BioTheranostics, outside the submitted work. Markéta Palácová has nothing to disclose. Sanjoy Chatterjee has nothing to disclose. Lakshmi Menon-Singh is an employee of Novartis Pharmaceuticals and holds stock or options to hold stock in the company. Jiwen Wu is an employee of Novartis Pharmaceuticals and holds stock or options to hold stock in the company. Miguel Martín received research grants from Roche, Puma Biotechnology, and Novartis; consulting/advisory fees from AstraZeneca, Amgen, Taiho Oncology, Roche/Genentech, Novartis, PharmaMar, Eli Lilly, Puma Biotechnology, Daiichi Sankyo, and Pfizer; and speaker's honoraria from AstraZeneca, Amgen, Roche/Genentech, Novartis, and Pfizer, outside the submitted work.

Ethical approval CompLEEment-1 was designed, implemented, and reported in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Harmonised Tripartite Guidelines for Good Clinical Practice, applicable local regulations, and the ethical principles laid down in the Declaration of Helsinki. The protocol and informed consent form were reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board before study commencement. A steering committee oversaw the trial conduct, as per the approved protocol. Representatives of the trial sponsor, Novartis Pharmaceuticals (East Hanover, NJ), collected and analysed the data.

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

Consent for publication Not applicable.

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