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ORIGINAL ARTICLE

A phase IV prospective study of efficacy and safety of ribociclib and letrozole as first-line therapy in older women (≥70 years) with hormone receptor-positive HER2-negative advanced breast cancer: the RibOB study

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Background: Cyclin-dependent kinase 4/6 inhibitors with endocrine therapy are standard first-line therapy for patients with hormone receptor-positive metastatic breast cancer. Older patients, especially the frailer subpopulation, are underrepresented in clinical trials, limiting data on treatment and safety outcomes in this population.

Patients and methods: The RibOB study was an open-label, single-arm phase IV prospective trial evaluating first-line ribociclib 600 mg 3 weeks out of 4 with letrozole in women ≥70 years with hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer. Primary endpoint was progression-free survival (PFS). Secondary endpoints were safety, functional evolution and quality of life (QoL), and outcomes in relation to clinical frailty assessed by G8.

Results: Seventy patients were enrolled: median age 76 years, with 30% ≥80 years. Forty-five out of 70 patients had a G8 score of ≤14 (frail) at baseline. With a median follow-up of 30.5 months, the median PFS was 36 months (95% confidence interval 24 months-not estimable). Median overall survival rate was not reached and breast cancer-specific survival rate at 24 and 36 months was 82% and 75%, respectively. Median time to treatment failure was 14.6 months. There were no significant differences in efficacy between fit and frail patients. Forty-seven out of 70 patients (67%) had grade 3 or higher adverse events, most commonly neutropenia (47%). Liver toxicity grade 3 or higher occurred in 2/70 (3%), and grade 3 or higher QT prolongation in 3/70 (4%). Thirty out of 70 patients (43%) discontinued ribociclib before progression and 57% required dose reductions to 400 mg, and 23% to 200 mg. Only 14 patients (20%) continued with the full 600-mg dose until end of study, disease progression, or death. No significant change in mean QoL was observed over time.

Conclusion: Ribociclib in combination with letrozole showed clear antitumor efficacy and safe treatment option in older patients with advanced breast cancer regardless of frailty. Frequent dose reductions and early discontinuation suggest the need for more research to optimize dosing in older patients.

Key words: advanced breast cancer, older patients, CDK4/6 inhibitor, frailty, toxicity

INTRODUCTION

Breast cancer (BC) is the leading cause of cancer deaths among European women, with 523 000 cases and 138 000 deaths in 2018.[1] In Belgium, 11 192 new cases were reported in 2022, making BC the most common cancer among women.[2] As populations age, older BC patients are

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increasing, often defined as ≥70 years in Belgium.[3,4] These patients face unique challenges like frailty, comorbidities, and different treatment priorities.[5,6] Despite recommendations for age-specific care and comprehensive geriatric assessment (CGA), older patients are often treated using general guidelines, with limited clinical trial data due to underrepresentation.[7,8] Experts stress the need for more research to create tailored treatment guidelines for this population.[9-11]

At least 70% of invasive BCs in older women are hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative, predominantly luminal A.[12,13] In metastatic patients, at least two sequential endocrine therapies (ETs) are the current recommendation but resistance will eventually occur.[14-17] ET combined with cyclin-dependent kinase 4/6 (CDK4/6) inhibitors has become the main first-line treatment strategy in patients with metastatic luminal BC.[18-22] Recent trials have established the effectiveness of ribociclib with ET in first-line and pretreated hormone receptor-positive metastatic BC (mBC) patients with consistent overall survival (OS) benefit in contrast to other CDK4/6 inhibitors.[23,24] However, data on their efficacy and safety in older patients remain limited.

Sonke et al.[25] conducted a dedicated analysis of patients aged 65 years or older ($n = 295$) who were included in the MONALEESA-2 study. Ribociclib in combination with letrozole was effective in this group [hazard ratio (HR) 0.61, 95% confidence interval (CI) 0.4-0.94], though the combination arm showed increased toxicity compared with letrozole with placebo, including neutropenia, fatigue, nausea, and diarrhea. Quality of life (QoL) was generally maintained, with improved pain scores for those receiving ribociclib.[26] While these findings are reassuring, the fitter nature of trial participants may not fully represent the broader real-world older population, where increased toxicity, functional decline, and issues like loss of cognition could be more pronounced.[11] Consequently, it remains unclear whether older patients benefit to a similar extent from CDK4/6 inhibitors plus ET, notably in real-life situations in which patients tend to have a higher burden of comorbidity and may be more frail than those included in clinical trials.

Older patients also prioritize their autonomy and avoid hospitalizations over extended survival. While ribociclib with letrozole is effective for patients with ER-positive/HER2-negative mBC, its suitability for frail older patients remains unclear due to potentially higher risks of toxicity and lower compliance.[27-29] To address this, we conducted a prospective study evaluating ribociclib plus letrozole in an unselected older population, focusing on functional status, QoL, and frailty—making it a unique study to include frailty assessments. We also evaluated efficacy and tolerance relative to patients' health, assessed through CGA.

PATIENTS AND METHODS

Study design and treatment

This is an observational prospective, multicentric, open-label, single-arm, phase IV trial conducted in 12 centers in Belgium (NCT03956654).

Oral letrozole (2.5 mg) was administered once daily continuously. Oral ribociclib 600 mg/day was administered on a 3-week-on 1-week-off schedule. Dosing of all study drugs was initiated on day 1 of the 28-day treatment cycle. Dose reductions for ribociclib (from 600 mg to 400 mg to 200 mg per day) were permitted to manage treatment-related adverse events; no dose reductions were allowed for letrozole. Patients who discontinued ribociclib were permitted to continue receiving letrozole. Treatment was continued until disease progression, death, intolerable toxicity, or patient/physician decision to withdraw.

Patients

Postmenopausal women 70+ years of age with locally confirmed, hormone receptor-positive, HER2-negative recurrent or *de novo* metastatic BC who had not received previous systemic therapy for advanced disease were eligible. Patients who received ≤28 days of aromatase inhibitor for advanced disease before inclusion were allowed.

Patients were excluded if they received any prior CDK4/6 inhibitor, in case of central nervous system (CNS) metastases (unless clinically stable and at least 4 weeks from prior therapy for CNS metastasis), or if they were at significant risk of developing QTc prolongation or impaired gastrointestinal function that altered drug absorption. Adequate bone marrow and organ function was required as per protocol (Supplementary Material, available at https://doi.org/10.1016/j.esmoop.2025.105896). The use of concomitant medications with a known risk of prolonging the QT interval or inducing torsades de pointes was not permitted.

Written informed consent was obtained from all patients at enrollment. The study protocol and any amendments were approved by the ethics committee at each participating site. The Supplementary Material includes further information on patient selection criteria and inclusion flow chart (Supplementary Table S1 and Figure S1, available at https://doi.org/10.1016/j.esmoop.2025.105896).

Endpoints

The primary endpoint related to efficacy was locally assessed progression-free survival (PFS), according to RECIST 1.1 criteria or death from any cause.

Secondary endpoints related to efficacy were time to treatment failure (TTF) (including disease progression, intolerance, and voluntary patient withdrawal), overall response rate (ORR) for patients with measurable disease as determined locally by investigator according to RECIST 1.1, OS, and breast cancer-specific survival (BCSS, length of time from the start of treatment and death from BC).

Secondary endpoints related to QoL and safety/tolerability were measured by the number of patients who experienced any adverse events (AEs); grade 3/4 AE; AE leading to dose reduction, interruption, or discontinuation; and serious AEs (SAEs), AEs of special interests (AESI), and AE-related deaths. AEs were defined according to ongoing reviews of all ribociclib safety data, including neutropenia, QT interval prolongation, and hepatobiliary toxicity.

Exploratory endpoints including aging biomarkers and thymidine kinase analyses are/will be presented in subsequent separate manuscripts.

Assessments

Tumor assessments were carried out using local radiological examinations at screening, at 12 weeks (±2 weeks) and 24 weeks (±2 weeks). Afterwards, radiological exams were carried out every 12-24 weeks (or longer), depending on the clinical need, as long as the patient was in study treatment phase or efficacy follow-up phase until progression, death, withdrawal of consent, lost to follow-up, or patient decision. There was no planned central review of imaging assessments.

AEs were characterized and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, v4.03 throughout the study (at each visit day 1 of every cycle), at unscheduled visits, and at the end of the treatment. Biochemical and hematological laboratory tests were done at screening, cycle 1 day 1 and 15, cycle 2 day 1, and all subsequent cycles and at the end of treatment. 12-lead electrocardiogram was done at cycle 1 day 1 and day 15 and cycle 2 day 1.

To evaluate the general health status, geriatric screening (GS) and geriatric assessment (GA) components and QoL were assessed at baseline, 12 weeks (±2 weeks), and at 48 weeks (±2 weeks).

GS was carried out by G8 to identify fit (G8 $>$ 14) and frail patients (G8 $\leq$ 14). The GA included social data (marital status, living situation, professional home care), functional status [activities of daily living (ADL), instrumental activities of daily living (IADL), and fall risk], fatigue (visual analogue scale), cognition (Mini-Cog), depression [Geriatric Depression Scale (GDS-15)], nutrition [Mini Nutritional Assessment-Short Form (MNA-SF)], polypharmacy, comorbidities (Charlson Comorbidity Index), and performance status (Eastern Cooperative Oncology Group performance status).

QoL was assessed using a modified version of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (QLQ-C30) questionnaire including global health status (GHS). Relevant items of the Quality of Life Questionnaire − Breast Cancer (QLQ-BR45) module for BC were added together with the ELD14 (elderly) module for older patients.

Statistical analysis

The Kaplan−Meier method was used to estimate the primary endpoint PFS and secondary endpoints TTF and OS with differences between fit and frail patients assessed using the log-rank test. The cumulative incidence function was applied to estimate BCSS, accounting for death of other causes as competing risks. For time-to-event outcomes with competing risks, covariate effects were analyzed using a cause-specific hazard model (Cox regression), ensuring that associations between predictors and outcomes were evaluated independently of competing events.

Cox proportional hazards regression models were employed to compare survival outcomes between fit and frail patients, with results reported as HRs and corresponding 95% CIs. Objective response rates were summarized using frequencies and percentages, with responder proportions estimated using 95% Wilson CIs. Comparisons between groups were conducted using the chi-square test.

For the endpoint, safety/tolerability [number (%) of AEs, grade 3/4 AEs; 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.

For the GS, GA, and QoL data, descriptive statistics were used to summarize the subscale and overall scores at each scheduled assessment time point. Additionally, change from baseline at the time of each assessment was summarized. For QoL assessments, linear mixed models were used for data analysis, incorporating a random intercept for each patient to account for the longitudinal data structure. The fixed effects structure included group (fit versus frail), time point, and group by time point interaction. Mean differences with 95% CI between groups were estimated at each time point as well as mean difference between time points per group. A Cox model evaluated the association between baseline QoL and OS, with results reported as HRs per 1-unit increase in QoL score (95% CI). A two-sample *t*-test compared mean baseline QoL between patients with and without grade III-IV ribociclib-related toxicity.

All analyses were conducted using SAS software (version 9.4, SAS System for Windows).

RESULTS

Baseline characteristics

From March 2019 to December 2022, a total of 70 patients were enrolled and available for efficacy follow-up (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2025.105896). Median age of participants at enrollment was 76.5 years, with 30% older than 80 years. Based on G8 scores, 25/70 were fit ($>$14) and 45/70 were frail ($\leq$14) at baseline. Thirty-seven percent of patients noted impairments in IADL; 34% scored dependent at ADL at baseline. Twenty percent of patients were possibly cognitively impaired based on a Mini-COG score at baseline. Forty-four percent of participants were at risk for malnutrition and 8.7% had malnutrition at baseline. Table 1 summarizes all baseline clinical, sociodemographic, and functional characteristics of included patients. Overview of medical history and information on BC history are provided in the supplementary section (Supplementary Tables S2-S4, available at https://doi.org/10.1016/j.esmoop.2025.105896). Forty-two patients had metastatic recurrence with a median time between diagnosis and metastasis of 16 years [interquartile range (IQR) 7.67-20.85 years].

Efficacy

With a median follow-up of 30.5 months (IQR 24.6-40.8 months), the median PFS for the entire cohort was 36.5 months [95% CI 24.1 months-not estimable (NE)]. No

Table 1. Patient, sociodemographic characteristics, and geriatric screening at inclusion

Variable	Operationalization	Patients included ($N = 70$), *n* (%)	Fit patients ($n = 25$), *n* (%)	Frail patients ($n = 45$), *n* (%)
Age (years)	70-74	23 (32.9)	10 (14.3)	13 (18.6)
	75-79	26 (37.1)	12 (17.1)	14 (20.0)
	80-84	17 (24.3)	3 (4.3)	14 (20.0)
	≥85	4 (5.7)	0	4 (5.7)
	Range	70-88	70-84	70-88
Polypharmacy	0-4 drugs	41 (58.6)	—	—
	≥5 drugs	29 (41.4)	—	—
CCI	Score 0	37 (52.9)	19 (27.1)	18 (25.7)
	Score 1-2	20 (28.6)	5 (7.1)	15 (21.4)
	Score 3-4	2 (2.9)	0	2 (2.9)
	Score ≥5	3 (4.3)	0	3 (4.3)
	Missing	8 (11.4)	1 (1.4)	7 (10.0)
ECOG PS	0	36 (51.4)	16 (22.9)	20 (28.6)
	1	28 (40.0)	8 (11.4)	20 (28.6)
	2	6 (8.6)	1 (1.4)	5 (7.1)
Stage at first BC diagnosis	I	10 (14.3)	4 (5.7)	6 (8.6)
	II	17 (24.3)	6 (8.6)	11 (15.7)
	III	9 (12.9)	3 (4.3)	6 (8.6)
	Stage unknown (non-metastatic)	6 (8.6)	1 (1.4)	5 (7.1)
	IV (metastatic)	28 (40.0)	11 (15.7)	17 (24.3)
Previous systemic therapy (in case of stage I, II, III, or unknown) ($n = 42$)	Yes	33 (78.6)	12 (28.6)	21 (50.0)
	No	9 (21.4)	2 (4.8)	7 (16.7)
Previous systemic treatment ($n = 33$) (several options together possible)	Chemo adjuvant	17 (51.5)	4 (12.1)	13 (39.4)
	Chemo neoadjuvant	2 (6.0)	0	2 (6.0)
	Endocrine adjuvant	27 (81.8)	9 (27.3)	18 (54.5)
	Endocrine neoadjuvant	2 (6.0)	0	2 (6.0)
	Target adjuvant	1 (3.0)	0	1 (3.0)
Measurable disease (RECIST 1.1) at baseline	Yes	52 (74.3)	—	—
	No (only non-measurable lesions)	18 (25.7)	—	—
Location of metastases (several options together possible)	Brain	3 (4.3)	3 (4.3)	0
	Visceral[a]	27 (81.8)	7 (10.0)	20 (28.6)
	Bone	44 (62.9)	18 (25.7)	26 (37.1)
	Peritoneum	1 (1.4)	0	1 (1.4)
	Lymph nodes (not locoregional)	17 (24.3)	5 (7.1)	12 (28.6)
	Locoregional	11 (15.7)	4 (5.7)	7 (10.0)
	Other	5 (7.1)	1 (1.4)	4 (5.7)
Geriatric screening				
G8 (0-17)	No geriatric risk profile (score >14)	25 (35.7)	25	0
	Geriatric risk profile (score 0-14)	45 (64.3)	0	45
Geriatric assessment				
Marital status	Single/divorced	11 (15.7)	5 (7.1)	6 (8.6)
	Married/legally cohabiting	34 (48.6)	11 (15.7)	23 (32.9)
	Widow	25 (35.7)	9 (12.9)	16 (22.9)
Living situation	Living at home alone	28 (40.0)	11 (15.7)	17 (24.3)
	Living at home with partner/family member/other	40 (57.1)	13 (18.6)	27 (38.6)
	Service flat/institution	2 (2.8)	1 (1.4)	1 (1.4)
Professional home care	No	35 (50.0)	13 (18.6)	22 (31.4)
	Yes	33 (47.1)	11 (15.7)	22 (31.4)
	Missing	2 (2.9)	1 (1.4)	1 (1.4)
FS: ADL (6-24)	Independent: score 6	46 (65.7)	20 (28.6)	26 (37.1)
	Dependent: score ≥7	24 (34.3)	5 (7.1)	19 (27.1)
Mini-COG (0-5)	Possibly cognitive impaired (score 0-2)	14 (20.0)	2 (2.9)	12 (17.1)
	Probably normal cognition (score 3-5)	50 (71.4)	21 (30.0)	29 (41.4)
	Missing	6 (8.6)	2 (2.9)	4 (5.7)
FS: IADL [0-8 (female)]	Independent: score 8 (female)	44 (62.9)	21 (30.0)	23 (32.9)
	Dependent: score <8	26 (37.1)	4 (5.7)	22 (31.4)
Falls history	Non-fallers	41 (74.5)[b]	19 (34.5)[b]	22 (40.0)[b]
	Fallers	14 (25.5)[b]	2 (3.6)[b]	12 (21.8)[b]
	Missing	15	4	11
Fatigue (VAS) (0-10)	No fatigue (score 0)	26 (37.1)	11 (15.7)	15 (21.4)
	Presence of fatigue (score 0.5-10)	41 (58.6)	12 (17.1)	29 (41.4)
	Missing	3	2	1
Nutrition (MNA-SF) (0-14)	Normal nutritional status (12-14)	33 (47.1)	21 (30.0)	12 (17.1)
	Risk of malnutrition (8-11)	30 (42.9)	4 (5.7)	26 (37.1)
	Malnutrition (0-7)	6 (8.6)	0	6 (8.6)
	Missing	1	0	1

Continued

Table 1. Continued

Variable	Operationalization	Patients included ($N = 70$), n (%)	Fit patients ($n = 25$), n (%)	Frail patients ($n = 45$), n (%)
BMI	Underweight (<18.5)	2 (2.9)	0	2 (2.9)
	Normal weight (18.5-24.9)	25 (35.7)	8 (11.4)	17 (24.2)
	Overweight (25-29.9)	26 (37.1)	11 (15.7)	15 (21.4)
	Obesity (>30)	16 (22.9)	6 (8.6)	10 (14.3)
	Unknown	1 (1.4)	0	1 (1.4)

ADL, activities daily life; BC, breast cancer; BMI, body mass index; CCI, Charlson Comorbidity Index; ECOG PS, Eastern Cooperative Oncology Group performance status; FS, functional status; IADL, Instrumental Activities of Daily Living; MNA-SF, Mini Nutritional Assessment—Short Form; VAS, visual analogue scale.
[a]Visceral involvement included liver, lung, and other visceral metastases.
[b]Percentage calculated on the denominator without missing.

statistically significant difference in PFS was observed between fit and frail patients (HR 1.25, 95% CI 0.62-2.53, $P = 0.53$).

Among 70 included patients, death during the study occurred in 19 patients (27%), while 51 patients (73%) were alive at the time of data analysis. The OS estimates at 12, 24, and 36 months were 91% (95% CI 81.2% to 95.9%), 82% (95% CI 70.2% to 89.3%), and 75% (95% CI 61.6% to 84.4%), respectively. The median OS has not been reached, with no significant difference between fit and frail patients (HR 0.82, 95% CI 0.31-2.15, $P = 0.68$). BC-specific death occurred in 18.6% of cases, while 8.6% of patients died due to other causes. The estimated BCSS rates were 96% at 12 months, 86% at 24 months, and 82% at 36 months. There was no significant difference in BCSS between fit and frail patients (HR 0.76, 95% CI 0.24-2.48, $P = 0.65$) (Figure 1).

The median TTF for the entire cohort was 14.6 months, with no significant difference between fit and frail patients (HR 0.99, 95% CI 0.55-1.80, $P = 0.98$). Among the fit group, 68% experienced treatment failure compared with 71% in the frail group. At 12 months, 52% of the fit group and 53% of the frail group remained on treatment. Median time on treatment was 15.4 months for the fit group and 13.8 months for the frail group (HR 0.99, 95% CI 0.55-1.80, $P = 0.98$).

Among the 52 patients with RECIST-measurable disease, the ORR—defined as the proportion of patients achieving partial response or complete response—was 58%. ORR was not significantly different between fit and frail patients: 68% in frail patients ($n = 34$) compared with 44% in fit patients ($n = 18$) ($P = 0.16$).

Safety—adverse events

Among the 70 assessable participants, 47 (67%) experienced a grade 3 or higher AE. The most frequent grade 3 or higher AE were neutropenia (47%), leukopenia (19%), lymphopenia (17%), dyspnea (9%), and fatigue (6%). Twenty-one out of 70 (30%) patients were hospitalized during the study. Grade 3 liver toxicity occurred in two patients (3%), grade 3 QT prolongation in three patients (4%), three patients developed interstitial lung disease (4%), two patients developed heart failure (3%), and one patient died on treatment due to a bronchopneumonia. All AEs are presented in Table 2. The occurrence of three grade 3 AE was not significantly higher in frail patients (33/45, 73%) than in fit patients (14/25, 56%) ($P = 0.14$) (Supplementary Table S5, available at https://doi.org/10.1016/j.esmoop.2025.105896).

The occurrence of grade 3 or higher AE was not significantly higher in frail patients (33/45, 73%) than in fit patients (14/25, 56%) ($P = 0.14$) (Supplementary Table S5, available at https://doi.org/10.1016/j.esmoop.2025.105896).

Ribociclib dose reductions and discontinuation

In our cohort, 30 out of 70 patients (43%) discontinued ribociclib before disease progression due to AE or patient's choice, with 14 of these patients stopping treatment without a prior dose reduction. Dose reductions were necessary for 37% of patients to 400 mg only, and for 20% of patients to 400 mg and then to 200 mg. Only 3% of patients went straight from 600 mg to 200 mg. Fourteen patients (five fit and nine frail, 20%) continued with the full 600-mg dose until the end of the study, disease progression, or death. Twenty-one out of 70 (30%) patients were on combination treatment at study end without progression or death. Median time to ribociclib discontinuation was 51 months in frail patients (95% CI 15.4 months-NE) versus 26 months in fit patients (95% CI 9 months-NE).

At 3 months, a significantly higher percentage of frail patients (47%) had required dose reduction compared with fit patients (28%). Frail patients had a 51% higher likelihood of dose reduction compared with fit patients within the first 3 months of treatment (HR 0.49, $P = 0.04$), whereas at the end of study, the proportion of patients who were still on the full 600-mg dose was 20% in both groups. Frail patients thus experienced dose reductions much earlier, with a median time to dose reduction of 3.9 months versus 39.4 months in the fit group (Figure 2).

QoL and functional status

The completion of the QLQ-C30 GHS questionnaire decreased from 99% ($n = 69$) at baseline to 83% ($n = 58$) at 12 weeks and to 53% ($n = 37$) at 48 weeks (Supplementary Figure S2, available at https://doi.org/10.1016/j.esmoop.2025.105896). GHS scores and QoL questionnaires indicated participants reporting stable global health throughout the treatment; mean scores and 95% CI of the GHS over time are shown in Figure 3A, and Supplementary Table S6, available at https://doi.org/10.1016/j.esmoop.2025.105896. The mean

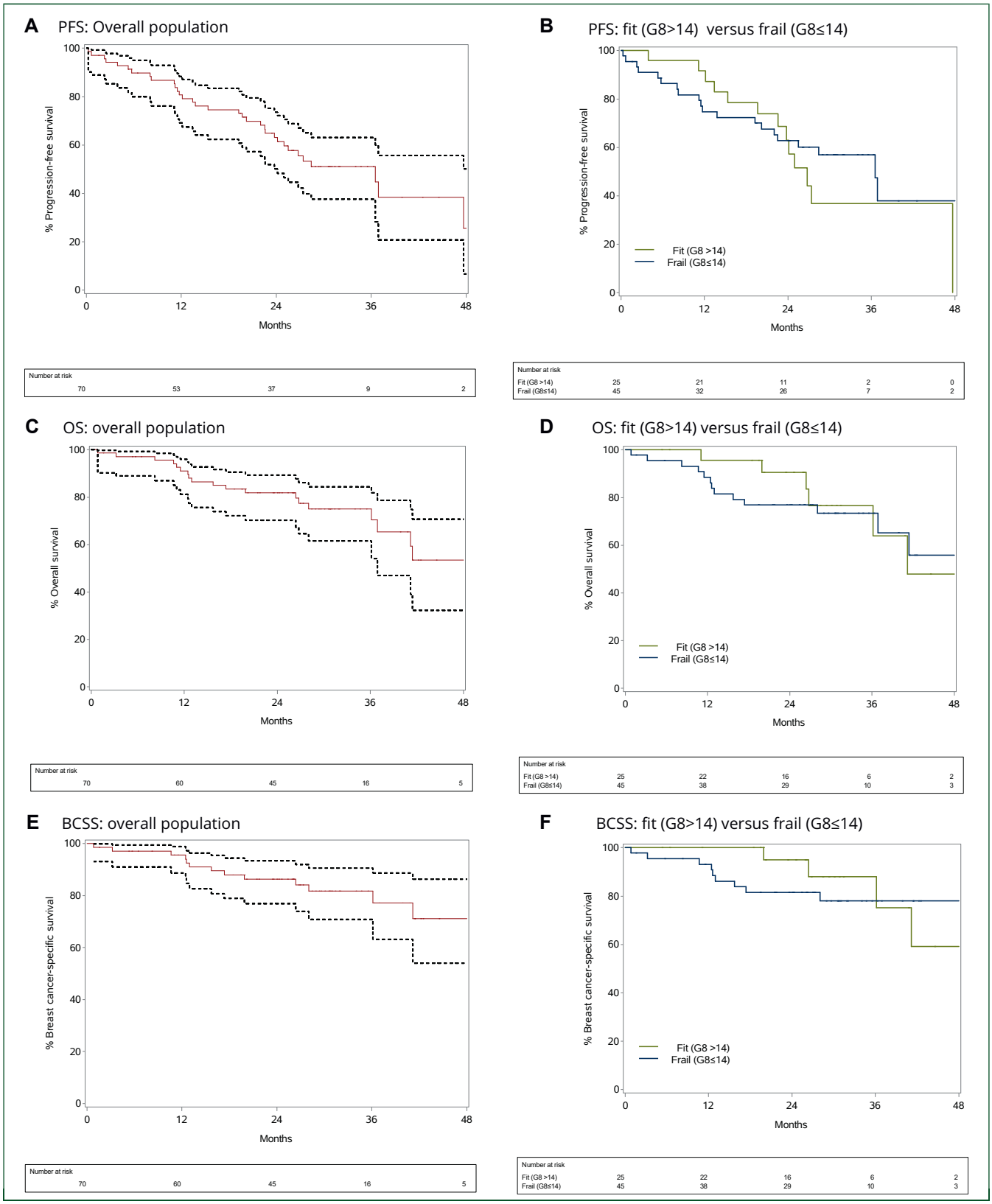

Figure 1. PFS, OS and BCSS in the overall population and fit versus frail patients. (A) Progression-free survival (PFS) in the overall population ($n = 70$), (B) PFS in fit (G8 $>$ 14) versus frail (G8 $\leq$ 14) patients, (C) overall survival (OS) in the overall population, (D) OS in fit (G8 $>$ 14) versus frail (G8 $\leq$ 14), (E) breast cancer-specific survival (BCSS) in the overall population, (F) BCSS in fit (G8 $>$ 14) versus frail (G8 $\leq$ 14) patients.

Table 2. Adverse events

AE	NCI CTCAE grade *N* = 70, *n* (%)				
	1	2	3	4	5
Neutropenia	9 (12.9)	21 (31.4)	30 (42.9)	3 (4.3)	0
Leukopenia	14 (20.0)	33 (47.1)	13 (18.6)	0	0
Lymphopenia	13 (18.6)	27 (38.6)	12 (17.1)	0	0
Anemia	34 (48.6)	13 (18.6)	3 (4.3)	0	0
Elevated creatinine	26 (37.1)	13 (18.6)	1 (1.4)	0	0
Fatigue	22 (31.4)	16 (22.3)	4 (5.7)	0	0
Nausea	27 (38.6)	5 (7.1)	0	0	0
Dyspnea	12 (17.1)	8 (11.4)	5 (7.1)	1 (1.4)	0
Thrombocytopenia	22 (31.4)	1 (1.4)	2 (2.9)	1 (1.4)	0
Alopecia	23 (32.9)	3 (4.2)	0	0	0
QTc prolongation	18 (25.7)	2 (2.9)	3 (4.3)	0	0
Elevated ALT	18 (25.7)	2 (2.9)	2 (2.9)	0	0
Anorexia	16 (22.9)	6 (8.6)	1 (1.4)	0	0
Constipation	22 (31.4)	1 (1.4)	0	0	0
Diarrhea	20 (28.6)	3 (4.3)	0	0	0
Rash	8 (11.4)	8 (11.4)	2 (2.9)	0	0
Edema	7 (10.0)	9 (12.9)	0	0	0
Cough	14 (20.0)	1 (1.4)	0	0	0
Dysgeusia	9 (12.9)	5 (7.1)	0	0	0
Muscle/joint pain	8 (11.4)	4 (5.7)	1 (1.4)	0	0
Vomiting	9 (12.9)	2 (2.9)	0	0	0
Headache	5 (7.1)	3 (4.3)	0	0	0
Itch	6 (8.6)	2 (2.9)	0	0	0
Pneumonia	1 (1.4)	0	2 (2.9)	0	1 (1.4)
ILD/pneumonitis	0	0	3 (4.3)	0	0
Heart failure	0	0	2 (2.9)	0	0
Pulmonary fibrosis	0	0	1 (1.4)	0	0
Diverticulitis	0	0	1 (1.4)	0	0
General status degradation	0	0	1 (1.4)	0	0

AE, adverse event; ALT, alanine aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events; ILD, interstitial lung disease; NCI, National Cancer Institute.

difference in GHS score between baseline and 12 weeks was 3.3 points (95% CI −2.0 to 8.7, $P = 0.22$), between baseline and 48 weeks was 3.8 points (95% CI: −2.4 to 10.1, $P = 0.23$). These results suggest no statistically significant change in mean GHS over the time points analyzed. The association between baseline GHS score and OS was not statistically significant (HR 0.99, 95% CI 0.97-1.01, $P = 0.21$).

Mean GHS scores were also compared between fit and frail patients. Statistical comparisons revealed no significant differences in the fit group between time points (Figure 3B). In frail patients, there was a significant increase in mean estimates from baseline to 48 weeks, with a mean difference of 10.7 points (95% CI 2.4-19.0, $P = 0.01$). The interaction P value for the difference in trends between fit and frail patients over time was 0.05, indicating a significant group effect. Due to the presence of missing data, these results should be interpreted with caution, as incomplete follow-up may have impacted the observed differences.

Supplementary Table S7, available at https://doi.org/10.1016/j.esmoop.2025.105896, shows results of GA at baseline and at 12 weeks and 48 weeks for all available patients. The GA scores indicated participants reporting stable functional and cognitive status throughout the treatment. There is a slight increase in fatigue scores. There was a slight trend of improvement in nutritional status.

DISCUSSION

This real-world study indicates that older patients with advanced or metastatic luminal BC starting letrozole and ribociclib have a long PFS of 36.5 months (95% CI 24.2 months-NE). This outcome compares favorably to the PFS of 25.3 months in the MONALEESA-2 trial (HR 0.57, 95% CI 0.46-0.70, $P < 0.001$) that included patients of all age.[23] A pooled analysis of patients ≥75 years ($n = 68$) from MONALEESA-2, -3, and -7[30] demonstrated a consistent PFS of 31 months (HR 0.54, 95% CI 0.34-0.86) and OS of 62 months (HR 0.75, 95% CI 0.46-1.21) in this age category. In older populations, tumors may progress more slowly, exhibiting a more indolent growth and spread.[31] This slower progression can delay the time to clinical progression or the need for additional treatment, leading to a longer PFS. In contrast, the global MONALEESA-2 trial may have included younger patients (mean 62 years) with more aggressive, faster-growing tumors, contributing to a shorter PFS.

Our data show a high survival rate in the first 2 years, with over 80% of patients still alive. However, by 48 months, just over half of the patients remain alive, indicating that survival starts to decline after 2 years. In the MONALEESA-2 trial, a median OS of 64 months (95% CI 52.4-71.0 months) was seen after 6.6 years of follow-up.[30] In our study, median OS was not reached due to short

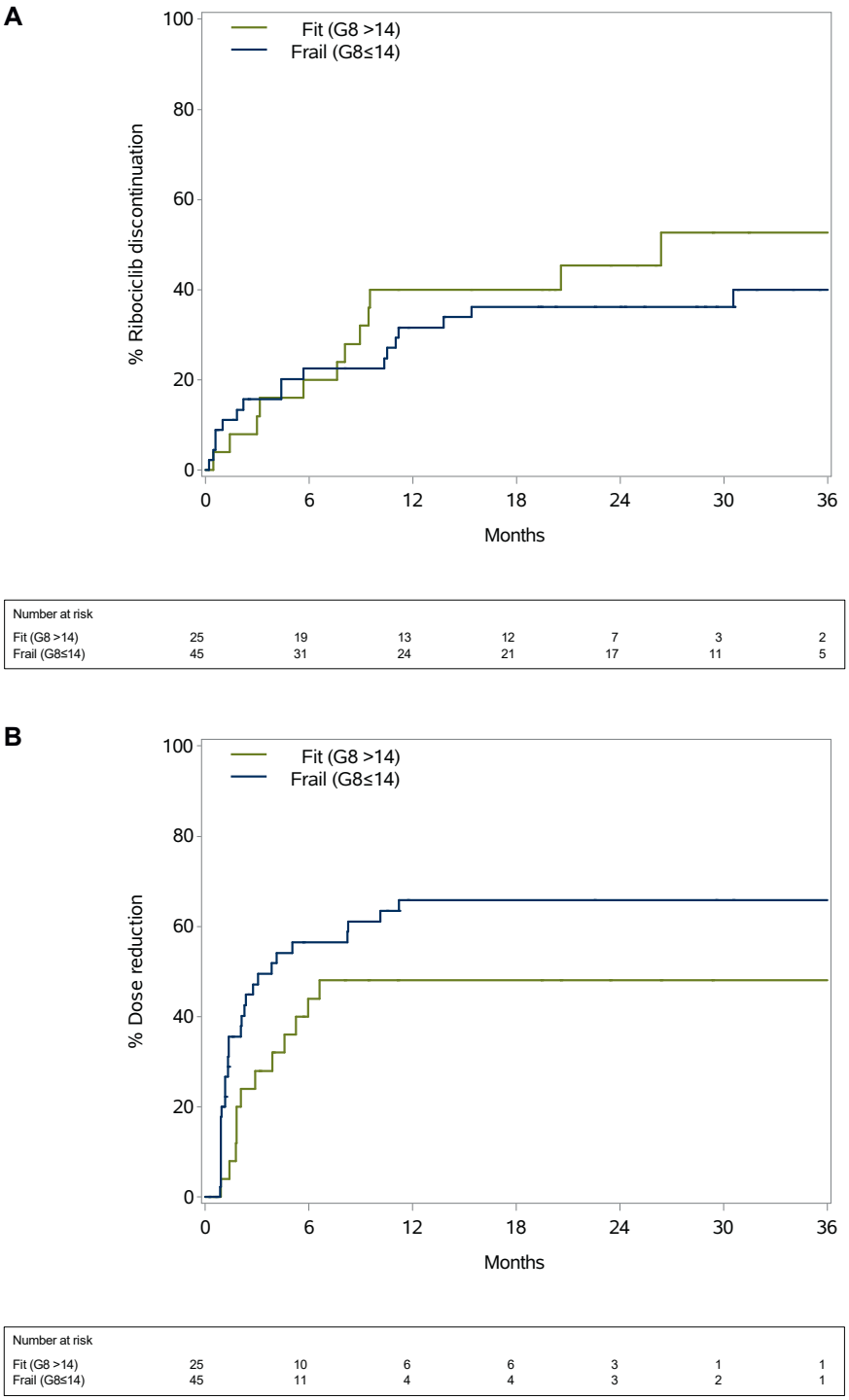

Figure 2. Discontinuation and dose reduction curve. (A) Ribociclib discontinuation curve in fit (G8 $>$ 14) versus frail (G8 $\leq$ 14) patients, and (B) dose reduction curve in fit (G8 $>$ 14) versus frail (G8 $\leq$ 14) patients.

follow-up; other real-world studies with CDK4/6 inhibitors in older patients have shown a lower OS in older patients.[32-35] This survival gap may partly be due to the frailty and age of the included patients and partly attributed to the strict protocol-specified definition of eligible patients for the MONALEESA trials, excluding individuals with poor performance status and comorbidities and less older patients. Moreover, although frail older adults represent a significant portion of the population undergoing anticancer treatment, their inclusion in clinical trials continues to be a challenge, even in studies with broader inclusion criteria.[36] Regardless of eligibility, patients with a history of cancer and comorbidities and those of advanced age (related to frailty) are less often invited to participate in trials.[37] Consequently, the trial populations selected may differ significantly from the diverse and frail patient groups

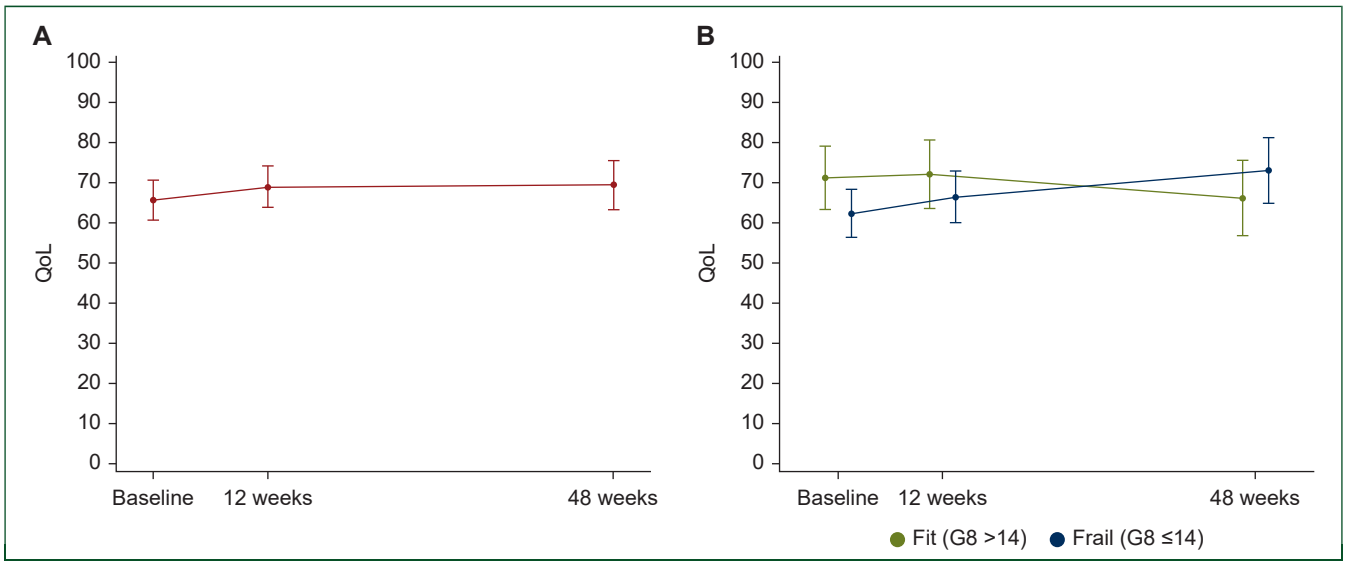

Figure 3. Mean global health scores with 95% CI over time in the overall population (A) and in fit (G8 > 14) versus frail (G8 ≤ 14) patients (B).
CI, confidence interval; QoL, quality of life.

typically treated in standard clinical practice.[38] Factors such as lower treatment adherence, decreased tolerability, and higher levels of comorbidities among patients treated in routine care may lead to a reduced OS compared with what is observed in clinical trials.

We found a large gap between PFS (36 months) and TTF (14.6 months) in this study, compared with a median duration of exposure to ribociclib of 20.2 months in the MONALEESA-2 trial.[23] This possibly reflects the difficulty many older patients face in tolerating treatment, leading to early discontinuation. This may be due to frailty, comorbidities, and a prioritization of QoL over continued therapy. We also need to consider that, after disease progression, there are limited effective treatments available for this population, or patients may choose not to pursue additional aggressive therapies.

Overall, the safety profile in this study was favorable. However, grade 3 or higher AEs were common (47/70 patients, 67%), primarily asymptomatic, laboratory-based hematological toxicities such as neutropenia (47%). These hematological toxicities did not frequently result in severe clinical consequences, such as febrile neutropenia, infection (isolated cases of grade 3 diverticulitis, two patients with grade 3 and one patient with grade 5 bronchopneumonia), or anemia-related symptoms (6% grade 3 fatigue). Gastrointestinal toxicities grade 3 or higher were rare, with no grade 3 or higher diarrhea or vomiting observed. Two patients experienced grade 3 liver enzyme elevation and another patient was hospitalized for liver toxicity.

These results align with findings from the MONALEESA-2 trial, which reported 87% grade 3-4 events in a slightly younger population (subanalysis in age group $\geq$65 years) treated with ribociclib.[25] The pooled analysis of MONALEESA 2-3-7 trials had 88% grade 3 or higher AEs in the $\geq$75-year-old group. The COMPLEEMENT-1 trial[39] similarly reported grade 3 or higher treatment-related AE in 68% of participants. Other studies, including the PALOMAGE[40] and Alliance A171601[35] trials, focused on older patients receiving palbociclib and endocrine therapy, further supporting the notion that CDK4/6 inhibitors are effective and manageable in this older population. Our study confirms that ribociclib is a safe treatment option for older and frail adults with hormone receptor-positive advanced BC, showing no unexpected toxicities. The rates of grade 3 or higher AEs were similar to those observed in younger patients.

In our cohort of older patients, 43% discontinued ribociclib before disease progression, and 57% required dose reductions to 400 mg or less due to AEs or patient's withdrawal. Only 14 patients (20%) continued with the full 600-mg dose until end of study, disease progression, or death. A pooled analysis of the MONALEESA trials[41] shows discontinuation due to AEs in 20% of patients in the 65- to 74-year age group and 41% in the $\geq$75-year age group. However, discontinuation was associated with a significantly higher risk of worse outcomes than for those who remained on treatment (HR 2.36, 95% CI 1.16-4.81, $P = 0.02$), reinforcing its negative impact on prognosis. Rates of dose interruptions, early discontinuations, and reductions to 400 mg were comparable between frail patients (G8 $\leq$ 14) and fit patients (G8 $>$ 14). However, frail patients required earlier (median time to dose reduction of 4 versus 39 months for fit versus frail patients, respectively) and more frequent reductions to the lowest dose of 200 mg and also experienced a numerically higher rate of grade 3 or higher AEs (73% versus 56%), suggesting lower overall tolerability. This trend may reflect increased physician caution in continuing treatment for frail patients experiencing AEs or requiring hospitalization. Interestingly, frail patients continued treatment longer (median 51 versus 26 months), potentially due to improved tolerability with dose reductions. These observations suggest that further evaluation may be warranted regarding the appropriateness of the currently approved starting dose of 600 mg for older patients. Frailty could potentially play a role in determining

optimal ribociclib dosing strategies in this population. Initiating treatment at 400 mg with the possibility of dose escalation in the absence of toxicity may represent a reasonable alternative for consideration. However, this approach requires additional investigation, acknowledging the challenges in securing funding for such studies.

The AMALEE study[42] investigated the efficacy of 600 mg versus 400 mg starting doses of first-line ribociclib in patients of all ages with hormone receptor-positive/HER2-negative advanced BC. The primary endpoint ORR was 42% (95% CI 34.4% to 48.7%) for the 400-mg dose and 45% (95% CI 38.1% to 52.6%) for the 600-mg dose. The ORR ratio for 400 mg versus 600 mg was 0.92 (90% CI 0.76-1.12). Although the results showed numerically similar response rates between the two doses, the lower bound of the 90% CI did not cross the prespecified noninferiority margin of 0.81. As a result, the study did not formally demonstrate statistical noninferiority of the 400-mg dose. It is important to note, however, that the trial was not powered to detect differences in subpopulations such as older adults or frail patients, and the overall similarity in efficacy may still support further exploration of lower starting doses in specific patient groups where tolerability is a great concern.

QoL and functional status were generally maintained in patients throughout this study. While no significant changes in GHS scores were observed over time within the fit group, frail patients showed a significant improvement in mean GHS score from baseline to 48 weeks, with an increase of 10.7 points (95% CI 2.4-19.0, $P = 0.012$). GA scores remained stable throughout this study with a trend to improvement in nutritional status. This QoL improvement suggests that frail patients perceived better overall health during treatment with ribociclib. Nevertheless, these findings should be interpreted cautiously, given the presence of missing data, particularly at the 12- and 48-week time points, which may have influenced the observed differences and introduced potential selection bias. Despite these limitations, the improvement in frail patients highlights the potential benefits of ribociclib in older and more vulnerable populations. This aligns with results of the RIBANNA trial.[43] Another argument in favor of CDK4/6 inhibitors is their ability to delay the need for chemotherapy, which is often associated with increased toxicity and a decline in QoL, particularly in older patients. By postponing chemotherapy, CDK4/6 inhibitors like ribociclib offer a therapeutic option that may help preserve the QoL and functional status in this vulnerable population.

We should also note that this study does not provide evidence that CDK4/6 inhibitors must be administered as first-line treatment for older patients, rather than reserving them for second-line use. Findings from the Dutch SONIA trial[44] indicate that, in women with hormone receptor-positive, HER2-negative advanced BC, using a CDK4/6 inhibitor in the first-line setting did not significantly extend the time from randomization to progression on second-line therapy (PFS2) or OS compared with delaying its use until the second line. However, first-line use of a CDK4/6 inhibitor did extend the time on the drug by 16.5 months, leading to a 42% increase in grade 3/4 toxicities and raising drug costs by ~$200 000 per patient. It is worth noting that the CDK4/6 inhibitor used in the SONIA trial was primarily palbociclib, which has recently been downgraded by the European Society for Medical Oncology's Magnitude of Clinical Benefit Scale, reflecting a more modest perceived benefit relative to ribociclib. For older patients, these findings support consideration of a second-line CDK4/6 inhibitor strategy, individualized based on overall health status, comorbidities, and patient preferences.

This study has limitations, including a small sample size (resulting in small numbers when comparing fit and frail subgroups, which can limit the power for intergroup comparisons), limited site representation, and no comparator arms for younger adults or other CDK4/6 inhibitors. Frailty classification was based on the G8 screening tool, which may overestimate frailty, as some patients with G8 $\leq$ 14 could be deemed fit following a GA. The specific reasons for ribociclib discontinuation stratified by health status (fit versus frail) were not systematically collected in a way that allows for meaningful subgroup analysis. Moreover, reasons for discontinuation may be multiple, and it is not always easy to narrow down to a single reason. Potential interventions, like pre-planned dose reductions, and interhospital variations in dose adjustments also warrant further investigation.

This study highlights the feasibility of trials for older adults with cancer and the need to close evidence gaps in this population. Future research should focus on optimizing dosing strategies to improve ribociclib tolerability in frail patients with advanced BC. The results of the IMPORTANT trial,[45] which investigates the use of GA to guide dose optimization of CDK4/6 inhibitors, are eagerly awaited.

In conclusion, ribociclib remains a good therapeutic option for older fit and frail patients with advanced BC. The high prevalence of comorbidities and low G8 scores in our representative cohort underscores the generalizability of these findings, as it captures a broader spectrum of patients commonly seen in routine care, including those who may be underrepresented in clinical trials due to frailty or advanced age. Ribociclib's toxicity profile in older patients is consistent with younger populations, with no unexpected major toxicities and with maintained QoL. Frequent dose reductions and early discontinuation suggest the need for more research to optimize dosing in older patients.

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