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Highlights

- Combination ribociclib and letrozole is a new standard first-line treatment option for hormone-positive, HER2-negative metastatic breast cancer, demonstrated by MONALEESA-2 trial
- KARMA, an Australian registry, is the first real-world study, developed alongside a Medicine Access Program, to report first-line ribociclib and AI treatment outcomes
- Our study found similar rates of dose reduction (56%) and treatment discontinuation (11%) due to toxicity as compared to MONALEESA-2
- This real-world registry cohort had a longer median duration of treatment (24.5 vs 20.2 months) and superior progression free survival (>36.5 vs 25.3 months) as compared to MONALEESA-2
- Real world evidence continues to be valued by clinicians to see drug tolerability and efficacy replicated in populations not always captured by trial settings

Real-world outcomes of ribociclib and aromatase inhibitor use in first line hormone receptor positive, HER2-negative metastatic breast cancer

Authors

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Abstract

Background: International guidelines recommend combining a CDK4/6 inhibitor and endocrine therapy (ET) as first line treatment for hormone receptor (HR) positive, HER2 negative metastatic breast cancer (MBC). Results from MONALEESA-2 demonstrate superior progression free survival

(PFS) and overall survival (OS) with ribociclib (CDK4/6 inhibitor) and ET compared to ET alone. Real world outcomes have yet to be reported.

Methods: KARMA is a non-interventional registry of Australian patients receiving first-line treatment with ribociclib and aromatase inhibitor (AI), obtained via a Medicine Access Program (MAP) for HR+, HER2- MBC. Outcomes were compared with the ribociclib/letrozole cohort in MONALEESA-2.

Results: Data from 160 patients at 17 sites was analysed. Median follow-up is 36.5 months. Compared to MONALEESA-2, patients were numerically younger (54.3 vs 62 years), with higher rates of bone-only metastases (31% vs 21%). 63 of 160 (39%) patients remain on treatment. 56% of patients had at least 1 dose reduction, with neutropenia (68%) and abnormal liver enzymes (17%) the most common reasons. 17 of 160 (11%) discontinued treatment due to toxicity, with no treatment related deaths. Median PFS was not reached (95% CI 29.9- NR), with PFS at 12 months and 18 months being 76% and 67% respectively versus 25.3 months, 73% and 63% in MONALEESA-2.

Conclusions: The ribociclib and AI combination was well tolerated in this real-world setting. The KARMA registry cohort achieved a superior PFS (>36.5 months) to MONALEESA-2, potentially due to more favourable baseline disease characteristics. Less frequent assessment scheduling in this non trial setting may also contribute.

Keywords:
Breast cancer, registries, medicine access programs

Introduction

Breast cancer is now the most common cancer diagnosed worldwide, with hormone receptor (HR+) positive, HER2 negative (HER2-) breast cancer accounting for nearly 70% of cases (1). In recent years, the combination of a CDK 4/6 inhibitor and endocrine therapy has transformed the treatment landscape of HR+ HER2- metastatic breast cancer (MBC) emerging as the new 'standard of care' first line treatment (2). First published in 2016, the MONALEESA-2 trial demonstrated improved median progression free survival (PFS) with ribociclib, a CDK4/6 inhibitor, plus letrozole compared to letrozole alone in a randomised population of 668 post-menopausal patients with HR+ HER2- MBC (3). More recently, the final protocol-specified analysis for MONALEESA-2 demonstrated a 12-month overall survival (OS) benefit (hazard ratio for death, 0.76; 95% CI, 0.63 to 0.93; two-sided P=0.008) for ribociclib and aromatase inhibitor (AI), marking the first and only CDK 4/6 inhibitor/AI combination to report an OS benefit in the first line post-menopausal HR+ HER2- MBC treatment setting (4).

Prior to ribociclib being government funded by the Australian Pharmaceutical Benefits Scheme (PBS), approximately 800 patients in Australia participated in a Novartis sponsored ribociclib compassionate medicine access program (MAP), run between May 2017 and June 2018, subsequently transitioning to PBS funded supply from July 2018. Despite the potential for valuable outcome data to be generated from patients who participate in MAPs, this data has traditionally not been collected due to many perceived challenges relating to ethics, data ownership, data security and patient privacy. However, our group has previously demonstrated the feasibility of successful data collection alongside a MAP, and that such a registry can yield valuable data on real world efficacy and safety (5).

To our knowledge there is limited published real-world data pertaining to treatment and outcomes for MBC patients treated with first line ribociclib and endocrine therapy, with no studies describing Australian practices. Patients routinely seen in the community setting often differ in critical factors

from those participating in clinical trials, including older age, presence of comorbidities, poorer performance status and living outside of the catchment of a tertiary cancer centre, all of these are often trial exclusion criteria. Thus, the external validity of clinical trial data remains uncertain with increasing importance on real-world studies to complement randomised controlled trial data. Real world data can provide information on safety and therapeutic effectiveness, better translating outcomes into routine clinical care. By establishing a registry alongside a MAP, we aimed to collect and describe the real-world patient and treatment outcomes of patients with HR+ HER2- MBC in Australia who received ribociclib in combination with an AI in the first-line setting.

Methods

KARMA (Kisqali Access Registry for Metastatic breast cancer in Australia) was established in August 2019 as a secondary data use, non-interventional study of Australian patients who received first line combination treatment of ribociclib obtained through the ribociclib MAP between May 2017 and June 2018, and an AI. Key eligibility criteria for the MAP mirrored that of the MONALEESA-2 study, i.e. post-menopausal women with HR+, HER2- MBC who had not received prior systemic treatment in the metastatic setting.

Clinicians from Australian hospitals who had enrolled patients in the ribociclib MAP were approached to gauge interest in study participation. De-identified patient data of enrolled patients were retrieved from medical records and entered onto an electronic REDCap case report form. Adverse events of special interest for this study included neutropenia, abnormal liver function tests and cardiac events (e.g. QT prolongation). Data with regards to dose reductions and drug discontinuations with rationale for these clinician decisions were also collected. Censor date of data was December 2020, allowing for a minimum of 30 month follow up for all patients from start date of treatment with ribociclib and aromatase inhibitor. Since this was an extremely low to negligible risk study and patient identifiers are not contained within the data collected, the study utilised a waiver of patient consent. This study and its reporting have been approved by the institutional Melbourne Health Human Research Ethics Committee.

The primary objective was to describe the real world clinical and tumour characteristics of patients with HR+ HER2- metastatic breast cancer in Australia who received ribociclib in combination with an aromatase inhibitor as part of the ribociclib MAP. The secondary objectives were to assess safety data including rates and reasons for dose interruptions and dose reductions of ribociclib, describe duration of treatment and progression free survival. Univariate and multivariate Cox analysis was performed with age ≥ 65 years, post-menopausal status, visceral metastases, de novo metastatic breast cancer, receipt of adjuvant chemotherapy, receipt of adjuvant endocrine therapy and endocrine therapy free interval as pre-specified variables. For relapsed patients, disease free interval was defined as time from primary cancer diagnosis to metastatic relapse, whilst endocrine therapy free interval was defined as time from cessation of adjuvant endocrine therapy to metastatic relapse. PFS was defined as time from commencement of line of treatment till confirmation of progressive disease. Where possible, direct comparisons were made with the ribociclib/letrozole cohort (n=334 patients) in MONALEESA-2. The exploratory objectives included investigating the natural disease trajectory of patients with HR+ HER2- MBC post disease progression, including clinician choice of second and third-line treatment and estimating PFS in immediate line of therapy post ribociclib and AI, where applicable. GraphPad Prism version 8, and Stata version 15 software was used to analyse the data. Overall survival and progression-free survival analyses used Cox proportional-hazards regression. Statistical significance was reported when $p<0.05$. No multiplicity adjustment was made for the analyses.

Results

167 patients from 17 sites who participated in the Novartis sponsored ribociclib compassionate MAP were enrolled into KARMA, with a median follow up of 36.5 months. Sites included major tertiary, metropolitan, regional, private and public centres. 7 patients were excluded from analysis with 2 patients found to be oestrogen-receptor negative, 4 patients having received ribociclib and AI as non first-line therapy for MBC and 1 patient receiving ribociclib and AI in the neoadjuvant treatment setting for early breast cancer. A total of 160 patients that met inclusion criteria were available for analysis.

Patient and disease characteristics

Table 1 demonstrates baseline patient and disease characteristics in KARMA, and where available, compared to MONALEESA-2's ribociclib/letrozole cohort. As compared to MONALEESA-2, patients in KARMA were numerically younger (54.3 vs 62 years) and there was a higher proportion of pre and peri-menopausal status (24% vs 0%). In addition, the KARMA cohort had numerically less disease burden (single site metastasis 61% vs 30%), with more bone-only metastases (31% vs 21%), and less visceral metastases (36% vs 59%). The distribution of ECOG status, oestrogen and progesterone positivity appeared similar, however data was incomplete.

Table 1: Baseline patient and disease characteristics

Baseline Characteristics	KARMA (n=160)	MONALEESA-2's ribociclib/letrozole cohort (n=334)
Age Mean (years) ≥ 65 years	54.3 (range 32-94 years) 32 (20%)	62 (range 23-91 years) Not available
Menopausal status at diagnosis of MBC Pre and peri-menopausal Post-menopausal Unknown	37 (24%) 121 (76%) 2 (1%)	0 334 (100%) 0
ECOG performance status • 0 • 1 • 2 or more • Unknown	88 (55%) 49 (31%) 5 (3%) 18 (11%)	205 (61%) 129 (39%) 0 0
Sites of metastases Bone • Any • Only Visceral Nodal Brain/leptomeningeal	104 (65%) 49 (31%) 58 (36%) 49 (31%) 6 (4%)	246 (74%) 69 (21%) 197 (59%) 133 (40%) 0
Number of metastatic sites 1 2 3+	97 (61%) 41 (26%) 22 (14%)	100 (30%) 118 (35%) 114 (34%)

Tumour characteristics	160 (100%)	332 (99%)
ER+	0	2 (1%)
• Positive	132 (83%)	271 (81%)
• Negative	21 (13%)	63 (19%)
PR+	7 (4%)	Not available
• Positive		
• Negative		
• Unknown		

Table 2 demonstrates the use of prior adjuvant therapy in the 118 patients with relapsed metastatic disease. Where available, data from KARMA was also compared to the 145 relapsed metastatic disease patients in the MONALEESA-2's ribociclib/letrozole cohort. Notably, 23 (19%) relapsed metastatic patients in KARMA had not received adjuvant endocrine therapy.

Table 2: Adjuvant therapy and disease-free interval in patients with relapsed metastatic disease

Characteristics	KARMA	MONALEESA-2's ribociclib/letrozole cohort
De novo metastatic disease	42 (26%)	114 (34%)
Relapsed metastatic disease	118 (74%)	220 (66%)
(Neo)Adjuvant chemotherapy*	74 (63%)	145 (66%)
Adjuvant endocrine therapy^	95 (81%)	Not available
• Total	72 (61%)	140 (64%)
• Tamoxifen	30 (25%)	34 (15%)
• Letrozole	38 (32%)	47 (21%)
• Anastrozole	9 (8%)	19 (9%)
• Exemestane	7 (6%)	6 (3%)
• Ovarian suppression		
Disease free interval	6 (5%)	4 (2%)
• <12 months	8 (7%)	14 (6%)
• 12-24 months	104 (88%)	202 (92%)
• >24 months		
Endocrine treatment free interval	37 (31%)	Not available
• <12 months (or relapsed on adjuvant endocrine therapy)	8 (7%)	Not available
• 12-24 months	47 (40%)	Not available
• >24 months	2 (2%)	Not available
• Unknown	1 (1%)	Not available
• Oophrectomy alone		

*Of those who received neo(adjuvant) chemotherapy, the most common regimens used were 5-fluorouracil, epirubicin, cyclophosphamide and docetaxel (FEC-D) 35%, followed by doxorubicin or epirubicin, cyclophosphamide and paclitaxel (AC/EC +T) 28%.

^Some patients received more than 1 adjuvant endocrine therapy

Treatment with ribociclib and aromatase inhibitor

At time of analysis, 63 of 160 (39%) patients remain on ribociclib and an AI. Median duration of treatment was 24.5 months, as compared to 20.2 months in MONALEESA-2's ribociclib/letrozole

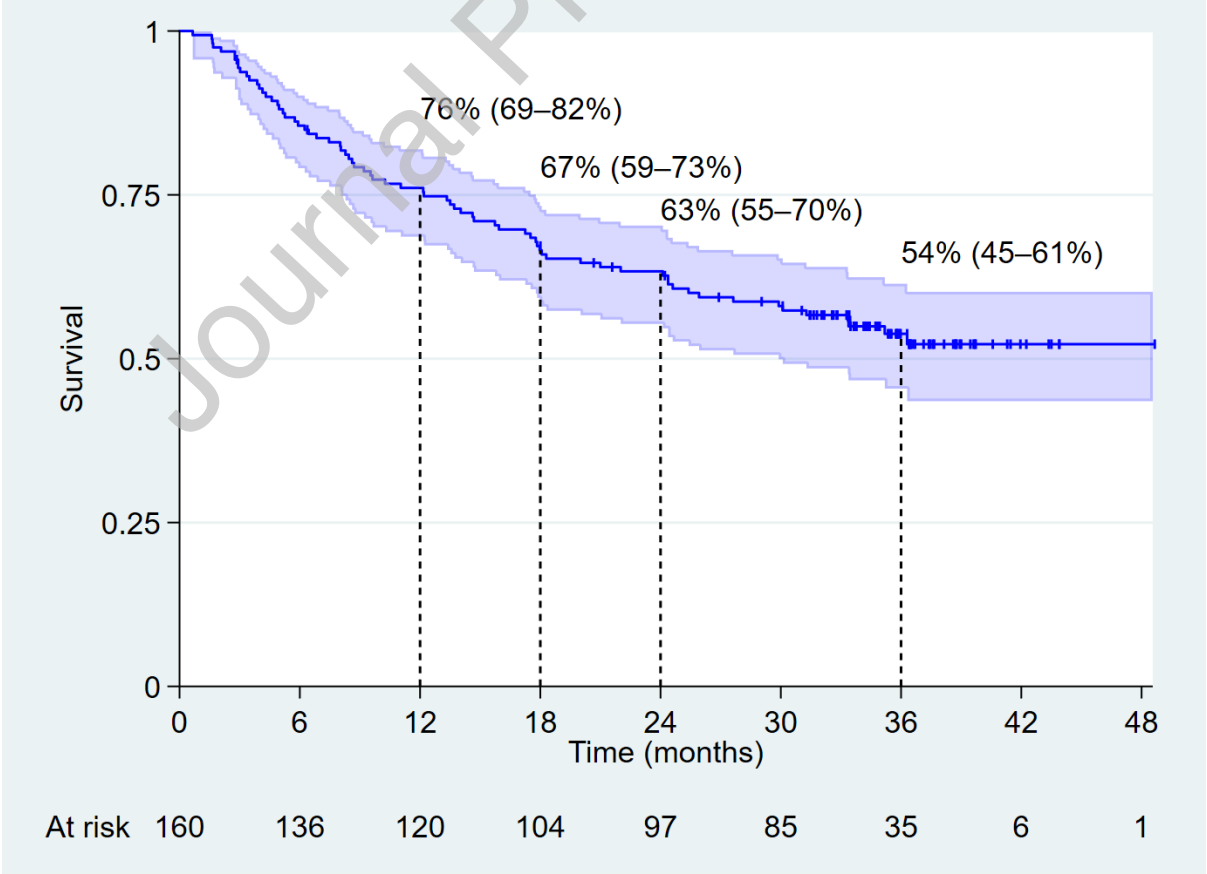
cohort. 85 (53%) patients in KARMA experienced at least one ribociclib interruption (versus 77% in MONALEESA-2), with the most common reason being neutropenia (54 of 85, 64%), followed by abnormal liver function tests (13 of 85, 15%). 4 patients (2.5%) had ribociclib interruption due to QTc prolongation. With regards to dose reductions, 90 (56%) patients experienced at least one ribociclib dose reduction (versus 54% in MONALEESA-2) with 71 (44%) patients required only one dose reduction and 19 (12%) two dose reductions. The most common reason for dose reductions was neutropenia (68%), followed by abnormal liver function tests (14%) and fatigue (8%). Other reasons included nausea and vomiting (2%), rash and pruritis (3%) and diarrhoea (2%).

97 of 160 (61%) patients discontinued ribociclib with 74 (46%) due to disease progression and 17 (11%) due to toxicity (versus 8% in MONALEESA-2). Of the 17 patients who experienced toxicity leading to drug discontinuation, this was due to abnormal liver function tests (n=6), fatigue (n=3), neutropenia (n=2), rash and pruritis (n=2), QTc prolongation (n=1), allergic reaction (n=1), headache (n=1) and infection (n=1). There were no deaths due to toxicity. The subsequent treatment for these 17 patients, included 4 patients with palbociclib and endocrine treatment, 9 patients continued on an AI alone, 2 commenced capecitabine and 2 did not receive any further active treatment.

Survival outcomes

At time of analysis, 45 of 160 (28%) patients had died. Median PFS was not reached (95% CI 29.9-NR), thus greater than the median follow up time of 36.5 months, as demonstrated in **Figure 1**. This is longer than MONALEESA-2 ribociclib/letrozole cohort's median PFS of 25.3 months (95% CI 23.0-30.3). Landmark PFS at 12 months and 18 months were 76% and 67% respectively as compared to 73% and 63% in MONALEESA-2.

Figure 1: Progression free survival



Univariate analysis and multivariate analysis for progression free survival was performed as pre-specified (Table 3 and Table 4). There was a trend that post-menopausal patients had improved PFS as compared to pre- or peri-menopausal patients (HR 0.59, p=0.06). There was also a trend that patients with de novo metastatic breast cancer (HR 0.47, p=0.06) and patients with an endocrine therapy free interval of > 12 months (HR 0.59, p=0.09) had an improved progression free survival when compared to patients with an endocrine therapy free interval of ≤ 12 months or who relapsed on adjuvant endocrine treatment.

Table 3: Univariate analysis for progression free survival

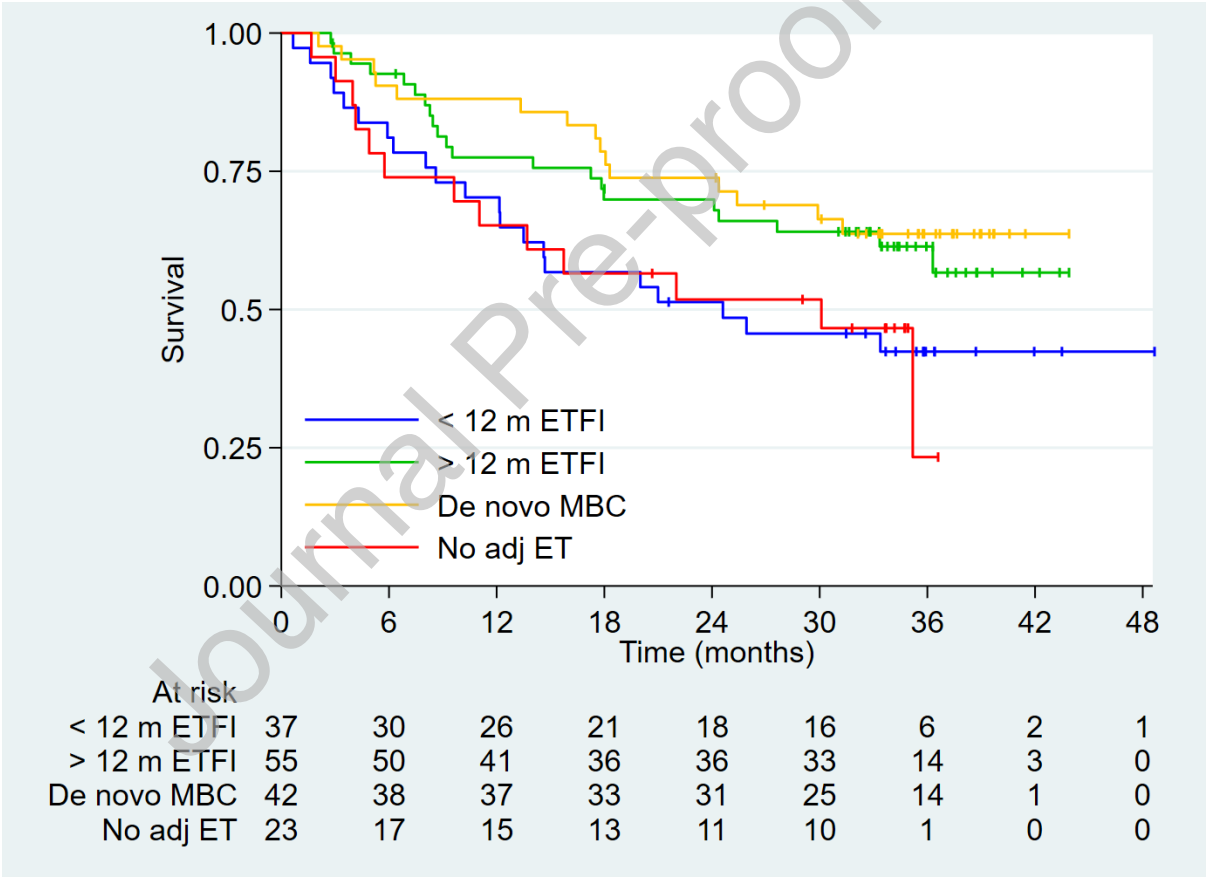
PFS	Hazard ratio	P	95% confidence interval	
Age ≥ 65 years	0.80	0.48	0.43-1.49	
Post-menopausal status	0.62	0.07	0.37-1.04	
Presence of visceral metastases	1.43	0.22	0.81-2.53	
Patients that received adjuvant chemotherapy	1.21	0.43	0.75-1.94	
Compared to patients that had an endocrine therapy free interval ≤ 12 months or relapsed on adjuvant endocrine therapy:				
Endocrine therapy free interval > 12 months	0.59	0.08	0.32-1.07	
Patients with relapsed breast cancer that did not receive adjuvant endocrine therapy	0.98	0.95	0.48-1.98	
Patients with de novo metastatic breast cancer	0.52	0.05	0.27-1.00	

Table 4: Multivariate analysis for progression free survival

PFS	Hazard ratio	P	95% confidence interval	
Age ≥ 65 years	1.00	1.00	0.51-1.97	
Post-menopausal status	0.59	0.06	0.34-1.03	
Presence of visceral metastases	1.52	0.16	0.85-2.72	
Patients that received adjuvant chemotherapy	0.99	0.98	0.56-1.75	
Compared to patients that had endocrine therapy free interval ≤ 12 months or relapsed on adjuvant endocrine therapy:				
Endocrine therapy free interval > 12 months	0.59	0.09	0.32-1.09	
Patients with relapsed breast cancer that did not receive adjuvant endocrine therapy	0.94	0.86	0.45-1.93	
Patients with de novo metastatic breast cancer	0.47	0.06	0.22-1.02	

Figure 2 demonstrates 4 subgroups of patients and first line PFS, (1) patients that had an endocrine therapy free interval of ≤ 12 months or relapsed on adjuvant endocrine therapy (n=37), (2) patients that had an endocrine therapy free interval > 12 months (n=55), (3) patients with relapsed breast cancer who did not receive adjuvant endocrine therapy (n=23), (4) patients with de novo metastatic breast cancer (n=42). Median PFS was 24.6 months, not reached, 30.1 months and not reached for subgroups 1,2,3 and 4 respectively. Landmark 12-month PFS and 24-month PFS were 70% and 51% for subgroup 1, 78% and 70% for subgroup 2, 65% and 51% for subgroup 3, 88% and 74% for subgroup 4 respectively.

Figure 2: Relapsed and de novo metastatic breast cancer subgroups in progression free survival



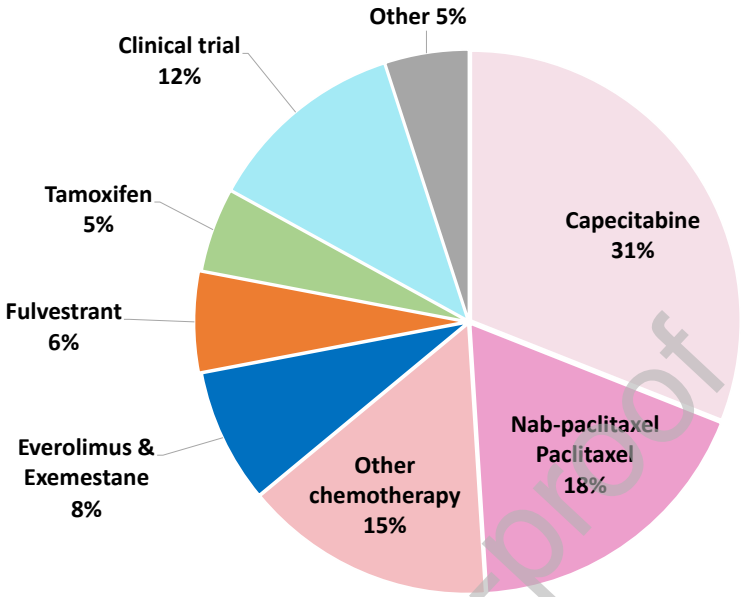
'<12m ETFI' = patients that had an Endocrine Therapy Free Interval ≤ 12 months or relapsed on adjuvant endocrine therapy, '>12m ETFI' = patients that had an Endocrine Therapy Free Interval > 12 months, 'No aET' = patients with relapsed breast cancer that did not receive adjuvant endocrine therapy, 'De novo MBC' = patients with de novo metastatic breast cancer

Subsequent treatment after disease progression

Of the 74 patients that had disease progression on first line ribociclib and an AI, 65 (88%) patients received second-line treatment. 3 patients died within 30 days of discontinuation of ribociclib and

aromatase inhibitor and 6 patients did not receive further systemic treatment. 42 of 65 (65%) patients received chemotherapy in the second-line treatment setting, with capecitabine being the most commonly prescribed regimen (Figure 3).

Figure 3: Second line treatment regimens



57 of 65 patients ceased second-line treatment with 51 due to disease progression and 4 patients ceased due to toxicity. Median overall second-line PFS was 4.7 months (95% CI 3.6-5.7 months). 44 of the 51 patients who developed disease progression on second-line treatment subsequently received third-line treatment with 36 (82%) receiving chemotherapy (capecitabine 44%, nab-paclitaxel 28%, eribulin 14% and other 14%), 2 (4%) everolimus and exemestane, 2(4%) fulvestrant, 2 (4%) olaparib and 2 (4%) were treated on a clinical trial.

Discussion

KARMA is a multi-centre Australian real-world study of ribociclib partnered with an AI captured alongside a Medicine Access Program in the first line treatment of HR+ HER2- metastatic breast cancer. This study indicates the safety and tolerability of the treatment combination with rates of drug interruptions, reductions and discontinuations in this setting is consistent with clinical trial data. The KARMA registry's median PFS of routine care patients on ribociclib and AI was numerically higher than that observed both in the post-menopausal ribociclib + letrozole cohort of MONALEESA-2 and the peri- and pre-menopausal ribociclib + endocrine therapy cohort of MONALEESA-7 (6). This study also provided valuable insight into the management of a subgroup of relapsed metastatic disease patients whose treatment outcomes may be impacted by the timing of progression following cessation of adjuvant endocrine therapy, as well as treatment selection in second line and beyond after progression on CDK4/6 inhibitor and AI in routine clinical practice. Moreover, the KARMA registry demonstrates the feasibility of comprehensive safety and efficacy data collection alongside a medicine access program.

As reported in the pivotal clinical trials, our study confirmed that the combination of ribociclib and AI is well tolerated by routine care patients with the main toxicities being neutropenia and liver function derangement. Clinically significant cardiac toxicity with QTc prolongation of more than 600

miliseconds led to treatment discontinuation in 1 of 160 patients which, which mirrors the results of 1% of the 1054 patients in combined MONALEESA-2, MONALEESA-3 (7), and MONALEESA-7 studies who also experienced a significant grade QTc interval prolongation (>500 miliseconds) (8). RIBANNA, an ongoing prospective, non-interventional study of German patients on first line treatment for HR+, HER2- advanced breast cancer, included 1016 patients at third interim analysis treated with ribociclib plus an AI or fulvestrant. Key all-grade adverse events for patients on ribociclib included neutropenia (19%), nausea (19%) and fatigue (17%), however, data has not been presented as to whether these have led to dose interruption, reduction or cessation (9). Two small real world studies of 28 and 31 patients (10, 11) reported on incidence of dose reductions and interruptions, mirroring our findings that ribociclib is safe to prescribe in routine care setting with associated cardiac toxicity appropriately managed with careful monitoring.

Our study suggested a numerically longer PFS of patients on ribociclib and an AI (>36.5 months) as compared to both MONALEESA-2 (25.3 months) and MONALEESA-7 (23.8 months). Notably, whilst the KARMA registry results were initially planned to be compared solely to MONALEESA-2, our study found that 1 in 4 patients enrolled were either pre or peri-menopausal which aligned with the patient population in MONALEESA-7. Potentially contributing to the observed numerically higher PFS is the KARMA registry's favourable baseline patient and disease characteristics (younger cohort, low burden of metastases and higher proportion of bone only metastases). Other potential explanations include less frequent or stringent restaging scans to monitor disease progression in routine practice as compared to strict pre-specified restaging scan windows in a clinical trials. An improved understanding of the optimal use of ribociclib (and other CDK 4/6 inhibitors) over time may have led to better patient selection as well as monitoring and management of adverse events. Real world studies of first-line CDK 4/6 inhibitor use (palbociclib and ribociclib) with endocrine therapies, have demonstrated a median PFS ranging from 18.7 – 21.3 months (12,13). Real world evidence for specifically palbociclib and AI in the first line setting have been reported with median PFS ranging from 13.3 – 29.4 months (). While there have not been any real-world studies thus far examining survival outcomes of ribociclib specifically with endocrine therapy in first-line setting, our novel KARMA registry study illustrates that the ribociclib and AI results in robust PFS outcomes in the first-line routine care setting.

In our multivariate subgroup analysis, there was a trend towards longer PFS among patients with an endocrine therapy free interval > 12 months (HR 0.59, p = 0.09) or de novo metastatic breast cancer patients (HR 0.47, p = 0.06) compared to those with an endocrine therapy free interval of < 12 months or those who relapsed on adjuvant endocrine therapy. Subgroup analyses from the MONALEESA-2 trial concluded that ribociclib is equally effective in patients who received prior endocrine therapy as compared to those who had not, however, patient endocrine therapy free interval data is not available for analysis (15). Although all subgroups appear to benefit from ribociclib and endocrine therapy in the MONALEESA-7 trial, the exploratory analysis in the most recent updated OS analysis suggests that patients who are not endocrine therapy naïve benefit from the treatment combination to a lesser degree (16,17). In a British real world retrospective study abstract examining use of CDK 4/6 inhibitors in combination with endocrine therapies (AI and fulvestrant), significantly poorer outcomes were demonstrated in patients that had an endocrine therapy free interval < 12 months as compared to those with an endocrine therapy free interval > 12 months (12.1 vs 28.4 months, HR 0.50 95%, CI 0.30-0.84) (13). Similarly, a Greek study demonstrated that 'endocrine-therapy resistant' patients treated with first line CDK 4/6 inhibitor and endocrine therapy had a shorter PFS than 'endocrine-therapy sensitive' patients (median PFS 18.1 months vs not reached) (14). Further research is required to demonstrate if patients with an endocrine therapy free interval of <12 months or who relapse on adjuvant endocrine therapy represent a poor prognostic subgroup, and if these patients would be better treated with upfront with a CDK 4/6 inhibitor and fulvestrant or with alternative first line treatment strategies.

Optimal therapy after first line use of CDK 4/6 inhibitors is largely unknown. Current treatment guidelines recommend at least two lines of endocrine-based therapies before sequencing onto chemotherapy (2,18). Our study found that of patients who progressed on first line ribociclib and AI and received second-line systemic therapy, around two-thirds received chemotherapy, with the preferred agent being capecitabine. Whilst sequential treatment data was not available for analysis from MONALEESA-2, in MONALEESA-7's ribociclib cohort, just under half of patients received chemotherapy in the second line setting with again the most common agent being capecitabine (17). Our study's real-world overall second-line median PFS was shorter than the duration of second-line treatment demonstrated in MONALEESA-7 (4.7 months vs 7.5 months). Plausible explanations include the older median age of patients in our study, or that a greater proportion of our patients were sequenced onto chemotherapy rather than endocrine therapies, potentially representing patients in the second-line setting with a greater disease burden. This trend was also seen in a US population-based study which suggested that patients transitioning from CDK 4/6 inhibitor first line therapy to chemotherapy, as compared to non-chemotherapy regimens, had a trend of being more likely to have rapidly progressing disease (19). Given this was an exploratory analysis, we did not investigate for number of sites of metastases prior to receipt of second-line systemic treatment. Further real-world evidence studies are required to explore outcomes of second-line chemotherapy agents after receipt of CDK 4/6 inhibitors.

Evidence for sequential non-chemotherapy options in patients who have progressed on first-line CDK4/6 inhibitors and AIs are limited as many therapies were developed in the pre CDK4/6 inhibitor era and little is known about potential cross-resistance (20). Our study demonstrated that clinicians favoured chemotherapy options in the second-line setting over non chemotherapy options, with everolimus and exemestane combination only compromising of 8% of second-line treatment regimens. Everolimus and exemestane combination as second line therapy was seen as the most common choice in an ongoing recruiting Canadian prospective real world observational study (21), with small scale retrospective studies demonstrating that efficacy and tolerability of everolimus and exemestane combination therapy is not affected by prior CDK 4/6 inhibitor use (22). Aside from the everolimus-exemestane combination, there are ongoing studies evaluating the potential benefit of continuing CDK4/6 inhibition and switching endocrine therapy at progression (23, 24), with the recently presented Phase 2 MAINTAIN trial demonstrating efficacy of fulvestrant or exemestane with ribociclib after progression on CDK4/6 inhibitor (25). For patients with PIK3Cα mutant tumours, use of alpelisib in combination with fulvestrant, after treatment with a CDK4/6 inhibitor demonstrated efficacy in the Phase 2 BYLieve study (26), with 50% PFS at 6 months. Further evolving research are examining mutational targets such as AKT (27) and ESR1 mutations (28), other novel oral selective oestrogen receptor degrader approaches such as HDAC inhibitors (29) and antibody drug conjugates such as sacituzumab govitecan (30). With ongoing extensive research into new targeted therapies for management of HR+ HER2- MBC patients, we suggest that continued monitoring of the uptake and outcomes of these therapies in the real-world setting remains integral to best practice.

Limitations of our study include that data was collected retrospectively and patients were not followed according to a strict protocol, which may have impacted the reported rates of adverse events and PFS. Data was only collected from a selection of sites that participated in the ribociclib MAP, potentially introducing a bias with respect to which patients were included. Moreover, despite the ribociclib MAP setting out clear eligibility criteria to mirror that of MONALEESA-2, inevitably a small proportion of community clinicians enrolled pre- and peri-menopausal patients on the MAP, reflecting real world practice.

Conclusion

First-line ribociclib and AI treatment for HR+ HER2- metastatic breast cancer in routine-care setting was safely delivered and well tolerated with similar rates of dose reductions and treatment discontinuations due to toxicity when compared to the clinical trial setting. This real-world registry cohort achieved a numerically higher median progression free survival as compared to MONALEESA-2, potentially explained in part by a younger population with more favourable baseline disease characteristics, including fewer disease sites and higher rates of bone-only metastases. Less rigid monitoring of disease progression may also have contributed. All subgroups including older patients, those with visceral metastases and receipt of prior adjuvant chemotherapy benefitted from first line treatment of ribociclib and AI. There was a trend for patients with an endocrine therapy free interval of <12 months and those who relapsed on adjuvant endocrine therapy to have a poorer prognosis. Our study further demonstrates the feasibility of comprehensive safety and efficacy data collection alongside a medicine access program and it is encouraging to find that drug tolerability and efficacy can be replicated in a non-trial patient population.

MicroAbstract

KARMA, a registry of patients who received first-line treatment with ribociclib and aromatase inhibitor (AI) for hormone receptor positive, HER2 negative metastatic breast cancer, was designed to analyse real-world treatment and survival outcomes. This study demonstrated that ribociclib and AI in this real-world clinical setting were well tolerated with encouraging survival data when compared to MONALEESA-2, the landmark clinical trial.

Clinical Practice Points

Over the last 5 years, combination CDK4/6 inhibitors and endocrine therapy (ET) have emerged as standard of care first line management of hormone receptor positive, HER2 negative metastatic breast cancer. Whilst large scale randomised clinical trials, such as MONALEESA-2, have demonstrated good treatment tolerability and superior survival outcomes for ribociclib and ET as compared to ET alone, there is limited outcome data in real-world clinical settings. KARMA is a secondary data use, non-interventional Australian registry of 160 patients who received first-line treatment with ribociclib and aromatase inhibitor (AI) for hormone receptor positive, HER2 negative metastatic breast cancer, collected alongside a ribociclib Medicine Access Program in Australia from 2017-2018. Ribociclib and AI treatment in real-world settings was well tolerated with similar rates of dose reduction (56 vs 54%) and treatment discontinuation due to toxicity (11 vs 8%) when compared to MONALEESA-2. The most common reasons for dose reduction were neutropenia (68%) and abnormal liver enzymes (17%), similar to that seen in the clinical trial setting. Moreover, the KARMA registry cohort achieved a superior median progression free survival as compared to MONALEESA-2 (>36.5 vs 25.3 months) potentially explained by this being a selected younger population with more favourable baseline disease characteristics, including fewer disease sites and higher rates of bone-only metastases and less rigid documentation of progression. This study provides further reassurance to clinicians that drug tolerability and efficacy of ribociclib in a pivotal clinical trial can be replicated in routine clinical practice.

Conflicts of Interest

Vanessa Wong has received speaker honoraria from Amgen and Janssen, and her affiliated institution is the recipient of research grant funding from Pierre-Fabre, Amgen, Roche, MSD, AstraZeneca and Merck. Richard de Boer is on the Australian advisory board for Eli Lilly, Novartis and Pfizer, received speaker honoraria from Novartis and Eli Lilly, and research funding from Novartis and Pfizer.
Katharine Cuff has received speaker honoraria from Novartis, is on the advisory board for Novartis, Pfizer and Ipsen, and is part of Amgen education support. Sheau Wen Lok's breast research team has received funding from Novartis, AstraZeneca, Roche and Amgen.

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