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ORIGINAL RESEARCH

Matching-adjusted indirect treatment comparison of ribociclib and palbociclib in HR+, HER2– advanced breast cancer

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Gabriel Tremblay[1]
David Chandiwana[2]
Mike Dolph[1]
Jaclyn Hearnden[1]
Anna Forsythe[1]
Mauricio Monaco[2]

[1]Purple Squirrel Economics, New York, NY, USA; [2]Novartis Pharmaceutical Corporation, East Hanover, NJ, USA

Background: Ribociclib (RIBO) and palbociclib (PALBO), combined with letrozole (LET), have been evaluated as treatments for hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer in separate Phase III randomized controlled trials (RCTs), but not head-to-head. Population differences can lead to biased results by classical indirect treatment comparison (ITC). Matching-adjusted indirect comparison (MAIC) aims to correct these differences. We compared RIBO and PALBO in hormone receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer using MAIC.

Methods: Patient-level data were available for RIBO (MONALEESA-2), while only published summary data were available for PALBO (PALOMA-2). Weights were assigned to MONALEESA-2 patient data such that mean baseline characteristics matched those reported for PALOMA-2; the resulting matched cohort was used in comparisons. Limited by the results reported in PALOMA-2, progression-free survival (PFS) was the primary comparison. Cox regression models were used to calculate adjusted hazard ratios (HRs) for PFS, before indirect treatment comparison (ITC) was performed with 95% confidence intervals. An exploratory analysis was performed similarly for overall survival using earlier PALBO data (PALOMA-1). Grade 3/4 adverse events were also compared.

Results: Racial characteristics, prior chemotherapy setting, and the extent of metastasis were the most imbalanced baseline characteristics. The unadjusted PFS HRs were 0.556 (0.429, 0.721) for RIBO+LET versus LET alone and 0.580 (0.460, 0.720) for PALBO+LET versus LET alone. MAIC adjustment resulted in an HR of 0.524 (0.406, 0.676) for RIBO+LET versus LET. PFS ITC using unadjusted trial data produced an HR of 0.959 (0.681, 1.350) for RIBO versus PALBO, or 0.904 (0.644, 1.268) with MAIC. Unadjusted overall survival HR of RIBO versus PALBO was 0.918 (0.492, 1.710); while exploratory MAIC was 0.839 (0.440, 1.598). ITC of grade 3/4 adverse events yielded a risk ratio of 0.806 (0.604, 1.076).

Conclusion: MAIC was performed for RIBO and PALBO in the absence of a head-to-head trial: though not statistically significant, the results favored RIBO.

Keywords: breast cancer, indirect treatment comparison, matching-adjusted indirect treatment comparison, ribociclib, palbociclib

Introduction

Breast cancer is the most prevalent cancer in women and is the second deadliest after lung cancer. An estimated 246,660 new cases of breast cancer were diagnosed in the USA in 2016 and an estimated 40,450 breast cancer deaths occurred. Approximately 12.4% of women will develop breast cancer over the course of their lifetime.[1] While breast cancer is detected at an early stage 90% of the time, many cases will progress

Correspondence: Gabriel Tremblay
Purple Squirrel Economics, 4 Lexington Ave, Suite 15K, New York, NY, USA
Tel +1 646 661 5496
Email gabrieltremblay@pshta.com

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to advanced or metastatic disease.[2,3] Once metastases are detected, the median survival rate is 18–24 months and fewer than 5% of patients are expected to be alive and disease-free after 5 years.[4] The most favorable prognosis is conferred to 74% of the patient population who have tumors that express hormonal receptors (HR+) and do not express human epidermal growth factor receptor 2 (HER2 [HER2−]). These tumors are more responsive to therapy than HR− tumors and less aggressive than HER2+ tumors.[5]

Postmenopausal women with HR+/HER2− advanced breast cancer (ABC) typically receive hormonal therapy (HT) as initial treatment.[6] The agents used include selective estrogen receptor antagonists tamoxifen and fulvestrant and aromatase inhibitors: exemestane, letrozole, and anastrozole.[7] Considering patients with advanced HR+ tumors, only 20%–40% respond to therapy initially and the majority will ultimately develop resistance.[8,9] Subsequently, HT may be used in combination with targeted therapy. Therapies that target pathways involved in resistance can restore or increase sensitivity to HT.[6] Everolimus and palbociclib (PALBO) are currently approved by the US Food and Drug Administration for the treatment for HR+/HER2− ABC in combination with aromatase inhibitors. In first- and second-line randomized controlled trials (RCTs), both agents have been shown to improve progression-free survival (PFS) compared with HT alone.[10,11]

Ribociclib (RIBO), a cyclin-dependent kinase (CDK) 4/6 inhibitor similar to PALBO, was evaluated in a Phase III clinical trial as first-line treatment for postmenopausal women with HR+/HER2− ABC. In the recent MONALEESA-2 trial, patients with HR+ HER2− ABC who received RIBO with letrozole (LET) had better PFS than those who received LET alone: median PFS was not reached in the RIBO arm at data cut-off whereas median PFS was 14.7 months in the placebo arm.[12] Patients in the RIBO and LET group experienced a 44% improvement in the risk of progression compared with those who received LET alone.[12]

Head-to-head comparison is an important tool to demonstrate treatment value and to aid decision-making. Accounting for the time required to perform a randomized trial, new agents may become available before they are compared with the relevant alternatives. Indirect treatment comparison (ITC), the statistical comparison of separate trials with like comparator groups, can provide timely evidence of comparative effectiveness. Guidelines and reviews of the methodologies now support the use of ITC, which is increasingly common.[13–15] However, there is an important consideration associated with this method: ITC compares non-randomized treatment groups. Classical ITC can, therefore, generate biased results when trials of variable design with different patient populations are compared. Recent refinements of the ITC methodology have focused on accounting for trial dissimilarities.

Matching-adjusted indirect comparison (MAIC) corrects for baseline differences in patient populations, allowing for indirect comparison with limited bias when patient level data are available for only 1 study. Where individual patient data are available, baseline characteristics can be adjusted and reweighted to match summary statistics for comparator population. The adjusted treatment outcomes may then be compared. This approach has provided strong comparative evidence in the absence of head-to-head studies in various disease settings.[14,16–19] RIBO and PALBO are CDK4/6 inhibitors demonstrated to be effective in HR+/HER2- ABC and so their comparison is clinically and economically relevant. As their corresponding trials used the same comparator – LET – and individual patient data were available for RIBO, MAIC was considered an appropriate methodology to examine comparative effectiveness.

Materials and methods

A systematic literature search following the guidelines published by the Cochrane Collaboration[22] and the UK's National Institute for Health and Clinical Excellence (NICE)[13] was conducted and identified 2 relevant Phase III RCTs and 1 relevant Phase II RCT: MONALEESA-2[12], RIBO and LET (CLEE011A2301 Clinical Study Report, Novartis Data on File); PALOMA-2[20], PALBO and LET; and PALOMA-1[10], PALBO and LET.[10]

MONALEESA-2 and PALOMA-2 both reported PFS as the primary endpoint. MONALEESA-2 reported overall survival (OS) as the secondary endpoint at the most recent cut-off (January 4, 2017). PALOMA-2 did not report mature results for OS, whereas the Phase II PALOMA-1 trial did. Hence, this analysis compared PFS results from MONALEESA-2 and PALOMA-2 and OS results from MONALEESA-2 and PALOMA-1.

ITC and MAIC statistical methods

To ensure the comparability of the trials, transitivity assumptions were tested according to the NICE Decision Support Unit (DSU) Technical Support Document 18 using a Population Average Treatment Effect (PATE) test.[13]

Classical frequentist ITC was performed using the Bucher (1997)[23] method with 95% confidence intervals (CIs). Treatment with LET and placebo was used as the common comparator to evaluate the efficacy of RIBO and LET versus PALBO and LET.

The adjusted baseline characteristics, selected based on feasibility and availability, were: age, race, region, Eastern Cooperative Oncology Group (ECOG) performance status, disease stage at diagnosis, disease-free interval (binary variable <12 months, i.e., de novo), current extent of disease using metastatic sites (visceral versus non-visceral binary variable), number of metastatic sites, and chemotherapy setting at baseline. Variable matching for PFS was performed: as patient level data were available for only the MONALEESA-2 trial, these data were adjusted and reweighted to match PALOMA-2 statistical data. First, the MONALEESA-2 trial population was modified to align its inclusion/exclusion criteria with the PALOMA-2 population. Some patients in the RIBO total intention-to-treat (ITT) dataset were excluded from this analysis based on PALOMA-2 exclusion criteria. In the second step of the MAIC analysis, the RIBO population data were reweighted such that the means/percentages of patient characteristics common to both datasets matched comparator data.

The weights were created by performing a logistic regression on the patient-level RIBO data that included an extra observation representing the comparator's data (i.e., a patient to whom the mean/percentage summarized values for the comparator's patient characteristics were attributed). The predicted values (or propensity score) that resulted from the logistic regression were used to weight the RIBO trial data (i.e., adjusted hazard ratios (HRs) were calculated using weighted Cox regression models).

Matching variables for OS using PALOMA-1 followed, although PALOMA-1 was a Phase II study and had slightly different baseline characteristics than PALOMA-2. The number of baseline characteristics reported in the publication was limited and matching could only be performed using a small number of variables. The following variables were available for matching OS in PALOMA-1 versus MONALEESA-2: median age, ECOG. Considering the matching limitations and the low number of OS events that have occurred to date in MONALEESA-2, OS is presented as an exploratory analysis.

Matching-adjusted ITC was performed according to NICE DSU guidelines.[13] Analyses were conducted using Stata (Version 13.1; StataCorp LP, College Station, TX, USA). Direct comparison of HRs for RIBO and PALBO was conducted and CIs were measured on a log scale.

Results

Design of the compared studies

The designs of MONALEESA-2 and PALOMA-2 are described in Table 1.

MONALEESA-2 and PALOMA-2 had different follow-up periods (~28 versus 23 months). However, the length of the follow-up period is unlikely to affect time-to-event endpoints, such as the HRs for PFS and OS, and was, therefore, not deemed to be a significant transitivity issue. The inclusion criteria for MONALEESA-2 and PALOMA-2/PALOMA-1 were deemed similar and the dosage of LET was identical. However, different stratification variables were used. MONALEESA-2 trial population was stratified according to the presence of lung and/or liver metastasis, while PALOMA-2 and PALOMA-1 populations were stratified by disease site and disease-free interval.

Patient characteristics

The designs of the MONALEESA-2 and PALOMA-2/PALOMA-1 trials were similar and were, therefore, considered suitable for comparison. Of the MONALEESA-2 ITT population, 334 patients were treated with RIBO and LET and 334 patients were treated with placebo and LET. In the PALOMA-2 trial, 444 patients were treated with PALBO and LET and 222 were assigned to the placebo and LET group. In the PALOMA-1 trial, 84 patients were treated with PALBO and LET and 81 were assigned to the LET group. Patient baseline characteristics are presented in Table 2.

Site of metastasis, adjuvant chemotherapy, patient age, and primary tumor size are strong prognostic factors in metastatic breast cancer.[21] As there was limited deviation in the PATE test, it was concluded that the data were robust enough to perform both an ITC (unmatched) and an MAIC with very little transitivity concern.

PFS

Patient characteristics common to both populations were matched, and the RIBO population was adjusted. Table 3 presents the levels of baseline characteristics (variables) in each population. The MONALEESA-2 population characteristics are also presented after adjustment to match PALOMA-2.

Median PFS was relatively consistent for the LET and placebo groups, with limited deviation from transitivity that would be potentially corrected by ITC and matching. Compared with LET and placebo, the unadjusted PFS HRs were 0.556 (0.429; 0.721) for RIBO and LET and 0.580 (0.460; 0.720) for PALBO and LET. MAIC with the PALOMA-2 population produced a PFS HR of 0.524 (0.407; 0.676) for RIBO and placebo. The unadjusted HR for RIBO versus PALBO was 0.959 (0.681; 1.350) while MAIC produced an HR of 0.904 (0.644; 1.268). Figure 1 depicts these results.

Table 1 Comparison of MONALEESA-2, and PALOMA-1 and -2

	MONALEESA-2[12]	PALOMA-2[20]	PALOMA-1[10]
Agent	Ribociclib (Novartis, Basel, Switzerland)	Palbociclib (Pfizer, New York, NY, USA)	Palbociclib (Pfizer, New York, NY, USA)
Study design	Allocation: randomized masking: double-blind	Allocation: randomized masking: double-blind	Allocation: randomized masking: open label
Inclusion criteria	Postmenopausal women with localized recurrent or metastatic cancer: ER+, HER2–, no prior systemic therapy for advanced disease, measurable disease per RECIST 1.1 or one predominantly lytic bone lesion, ECOG 0–1	Postmenopausal women with localized recurrent or metastatic cancer: ER+, no prior systemic therapy for ER+ cancer, measurable disease per RECIST or bone only disease, ECOG 0–2, adequate organ/marrow function	Postmenopausal women with localized recurrent or metastatic cancer: ER+, HER2–, no previous treatment for advanced disease, measurable disease per RECIST or bone only disease, ECOG 0–1, adequate organ/marrow function
Exclusion criteria	Prior treatment with a CDK inhibitor, prior systemic therapy, concurrent use of another anti-cancer therapy, concurrent malignancy or malignancy within 3 years of randomization, active cardiac disease or history of dysfunction, systolic blood pressure >160 or <90 mmHg, patients receiving certain medications that cannot be discontinued	HER2+, patients at risk of life-threatening complications in the short term, known uncontrolled or symptomatic CNS metastases, prior treatment with letrozole/anastrozole with DFI ≤12 months from completion of treatment, prior treatment with a CDK inhibitor	Previous treatment for advanced disease, prior treatment with letrozole as either neoadjuvant or adjuvant treatment within the 12 months before study entry, any previous treatment for advanced breast cancer, brain metastasis, or previous treatment with a CDK inhibitor
Enrollment	668	650 (estimated)	165
Experimental arm	600 mg LEE011 orally (3 weeks on/1 week off) in combination with once daily 2.5 mg letrozole	125 mg PD-0332991 orally (3 weeks on/1 week off) in combination with once daily 2.5 mg letrozole	125 mg PD-0332991 orally (3 weeks on/1 week off) in combination with once daily 2.5 mg letrozole
Comparator arm	Placebo orally (3 weeks on/1 week off) in combination with once daily 2.5 mg letrozole	Placebo orally (3 weeks on/1 week off) in combination with once daily 2.5 mg letrozole	Once daily 2.5 mg letrozole tablets on a continuous regime
Primary outcome measure	PFS, time frame: up to 20 months	PFS, time frame: baseline up to 2.5 years	PFS, time frame: assessed up to 41 months
Secondary outcome measures	OS: up to 65 months	OS: up to 6 years	OS: up to 41 months (median)

Notes: Outcome measures irrelevant to this study are not listed.
Abbreviations: CDK, cyclin-dependent kinase; DFI, disease-free interval; ECOG, European Cooperative Oncology Group (performance status); ER+, estrogen receptor-positive; HER2–, human epidermal growth factor 2-negative; HER2+, human epidermal growth factor 2-positive; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria In Solid Tumors.

Table 2 Patient characteristics

Patient characteristics	Ribociclib (MONALEESA-2)[12]		Palbociclib (PALOMA-2)[20]		Palbociclib (PALOMA-1)[10]	
	RIBO+LET	PBO+LET	PALBO+LET	PBO+LET	PALBO+LET	LET
Age criteria	≥18		NR (postmenopausal)		≥18 (postmenopausal)	
Median age	62	63	62	61	63	64
Age: ≥65	45%	43%	41%	37%	NR	NR
Race						
White	80.5%	83.8%	77.5%	77.5%	NR	NR
Black	3.0%	2.1%	1.8%	1.4%	NR	NR
Asian	8.4%	6.9%	14.6%	13.5%	NR	NR
Native American	0.3%	0%	NR	NR	NR	NR
Pacific Islander	0.3%	0%	NR	NR	NR	NR
Other	3.6%	2.4%	6.1%	7.7%	NR	NR
Unknown	3.9%	4.8%	NR	NR	NR	NR
Region						
North America	32.3%	36.2%	37.8%	44.6%	NR	NR
Non-North America	67.7%	63.8%	62.2%	55.4%	NR	NR
ECOG:						
0	61.4%	60.5%	57.9%	45.9%	55%	56%
1	38.6%	39.5%	40.1%	52.7%	45%	44%
2	0%	0%	2.0%	1.4%	0%	0%
3	0%	0%	0%	0%	0%	0%
4	0%	0%	0%	0%	0%	0%

(*Continued*)

Table 2 (*Continued*)

Patient characteristics	Ribociclib (MONALEESA-2)[12]		Palbociclib (PALOMA-2)[20]		Palbociclib (PALOMA-1)[10]	
	RIBO+LET	PBO+LET	PALBO+LET	PBO+LET	PALBO+LET	LET
Primary site of cancer:						
Breast	100%	100%	100%	100%	100%	100%
Histological grade:						
Well differentiated	9.0%	10.5%	NR	NR	NR	NR
Moderately differentiated	42.8%	38.3%	NR	NR	NR	NR
Poorly differentiated	17.7%	22.5%	NR	NR	NR	NR
Undifferentiated	0.9%	1.5%	NR	NR	NR	NR
Unknown	29.6%	26.6%	NR	NR	NR	NR
Missing	0%	0.6%	NR	NR	NR	NR
Stage at initial diagnosis:						
0	2.1%	1.8%	0%	0%	NR	NR
I	16.5%	14.4%	11.5%	13.5%	NR	NR
II	29.3%	32.0%	30.9%	30.6%	NR	NR
III	17.4%	18.6%	16.2%	17.6%	NR	NR
IV	34.4%	32.3%	31.1%	32.4%	NR	NR
Unknown/missing	0.3%	0.9%	10.4%	5.9%	NR	NR
Stage at study entry:						
III	0.3%	0.9%	NR	NR	2%	1%
IV	99.7%	99.1%	NR	NR	98%	99%
Time since initial diagnosis of primary site (median months)	58.1	52.1	NR	NR	NR	NR
Disease-free interval:						
De novo	34.1%	33.8%	37.6%	36.5%	52%	46%
Non-de novo	65.9%	66.2%	62.4%	63.5%	48%	54%
Types of lesions at baseline:						
Target only	9.6%	8.4%	NR	NR	NR	NR
Non-target only	23.1%	26.3%	NR	NR	NR	NR
Both target and non-target	67.1%	65.0%	NR	NR	NR	NR
Unknown	0.3%	0.3%	NR	NR	NR	NR
HER2 receptor status:						
Positive	0.3%	0.3%	0%	0%	0%	0%
Negative	99.7%	99.7%	100%	100%	100%	100%
Estrogen receptor status						
Positive	99.4%	99.7%	100%	100%	100%	100%
Negative	0.6%	0.3%	0%	0%	0%	0%
Progesterone receptor status						
Positive	81.1%	83.2%	NR	NR	NR	NR
Negative	16.5%	14.7%	NR	NR	NR	NR
Unknown	2.4%	2.1%	NR	NR	NR	NR
Estrogen and/or progesterone receptor status	100%	100%	100%	100%	100%	100%
At least one positive						
Current extent of disease (metastatic sites)	2.4%	3.3%	NR	NR	NR	NR
Breast	0%	0.6%	NR	NR	NR	NR
Bone marrow	73.7%	73.1%	NR	NR	20%	15%%
Bone	59.0%	58.7%	48.2%	49.5%	44%	53%
Visceral	4.5%	3.0%	NR	NR	NR	NR
Skin	39.8%	36.8%	NR	NR	NR	NR
Lymph nodes	6.0%	3.0%	NR	NR	NR	NR
Others	0.6%	0.3%	NR	NR	NR	NR
None	NR	NR	51.8%	50.5%	36%	32%
Total non-visceral						
Number of metastatic sites involved						
0	0.6%	0.3%	NR	NR	NR	NR
1	29.9%	35.0%	31.1%	29.7%	NR	NR
2	35.3%	30.8%	26.4%	23.4%	NR	NR
>2	34.2%	33.9%	42.5%	46.9%	NR	NR

Abbreviations: ECOG, European Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; LET, letrozole; NR, not reported; PALBO, palbociclib; RIBO, ribociclib.

Table 3 Patient characteristics before and after adjustment (in "levels")

Variable	Level in MONALEESA-2[12] before matching	Level in PALOMA-2[20]	Level in MONALEESA-2 after matching
Age	61.594	61.667	61.667
Age group: ≥65	0.441	0.397	0.397
Race: White	0.822	0.775	0.775
Asian	0.078	0.142	0.142
Black	0.026	0.017	0.017
Region: North America	0.343	0.401	0.401
ECOG 1	0.392	0.479	0.479
Prior chemo setting: adjuvant	0.379	0.404	0.404
Prior chemo setting: neoadjuvant	0.100	0.129	0.129
Prior hormonal setting: adjuvant	0.518	0.563	0.563
Stage 3+ at diagnosis	0.527	0.529	0.529
Metastatic sites (0–2)	0.659	0.560	0.560
Disease-free interval (de novo)	0.370	0.372	0.372
Visceral metastases	0.591	0.486	0.486

Notes: Differences of ≥10% are highlighted in gray.
Abbreviations: ECOG, European Cooperative Oncology Group; chemo, chemotherapy.

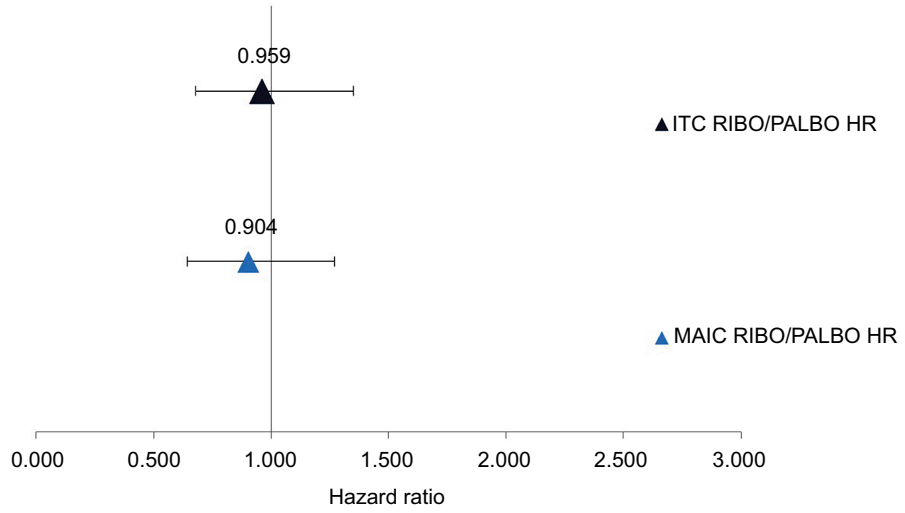

Figure 1 Progression-free survival for RIBO versus PALBO with and without matching adjustment.
Notes: HR <1 favors RIBO, >1 favors PALBO.
Abbreviations: HR, hazard ratio; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect treatment comparison; PALBO, palbociclib; RIBO, ribociclib.

Regarding the statistical fitting of the matching, the estimate had a relatively small R-square value for this type of regression: a pseudo R-square of 0.0251 (prob >χ^2=1). Akaike information criterion (AIC) and Bayesian information criterion (BIC) statistics are valuable when comparing models. In this case, the AIC and BIC were 44.58 and 111.78 respectively, which indicates a moderate fit. The relatively large number of matching variables explains the difference in AIC and BIC, which could suggest overmatching. The MONALEESA-2 population was reduced by about 30% in each arm to fit the PALOMA-2. Compared with the ITT population, the effective sample size was 66% for RIBO and 71% for placebo (postexclusion sample sizes were 68% and 73%, respectively), indicating moderate fit.

OS

Exploratory unadjusted and adjusted comparisons of OS were performed. As OS data from PALOMA-2 were unavailable, data for PALBO were obtained from the Phase II PALOMA-1 trial. Compared with LET and placebo, the unadjusted OS HRs were 0.746 (0.517; 1.078) for RIBO and LET and 0.813 (0.492; 1.345) for PALBO and LET. MAIC with the PALOMA-1 population produced an OS HR of 0.682 (0.456; 1.021) for RIBO and placebo. The unadjusted HR for RIBO versus PALBO was 0.918 (0.492; 1.710) while MAIC produced an HR of 0.839 (0.440; 1.598). The HR results of this analysis are presented in Figure 2.

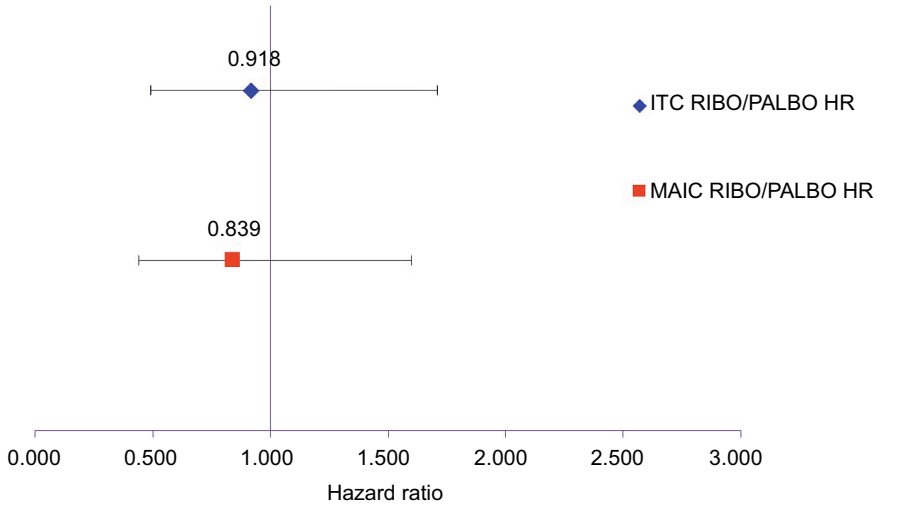

Figure 2 Overall survival for RIBO versus PALBO with and without matching adjustment.
Notes: HR <1 favors RIBO, >1 favors PALBO.
Abbreviations: HR, hazard ratio; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect treatment comparison; PALBO, palbociclib; RIBO, ribociclib.

Grade 3/4 adverse events

The ITC of grade 3/4 adverse events yielded a risk ratio of 0.806 (0.604; 1.076; Table 4), indicating a trend of fewer severe adverse events with RIBO.

Table 4 Indirect treatment comparison of grade 3/4 adverse events

	Treatment	Control	Risk ratio (95% CI)
Grade 3–4 adverse events			
Direct	Ribociclib	Placebo	2.509 (2.130–2.955)
comparison	Palbociclib		3.111 (2.452–3.947)
ITC	Ribociclib	Palbociclib	0.806 (0.604–1.076)

Abbreviation: ITC, indirect treatment comparison.

Discussion

An analysis was performed to determine the efficacy of RIBO compared with PALBO for the treatment of HR+/HER2− ABC. This analysis compared PFS and OS in Phase II/III trials of RIBO or PALBO and LET treatment with and without matching adjustment.

In MONALEESA-2, RIBO plus LET was shown to improve PFS versus LET alone.[12] The MONALEESA-2 PFS HR for RIBO and LET treatment versus LET alone decreased following matching to the PALOMA-2 trial population data: an HR of 0.556 (0.429; 0.721) became 0.524 (0.406; 0.676). RIBO, therefore, demonstrated improved results in the PALOMA-2 context compared with the MONALEESA-2 context. Upon comparison by classical ITC, RIBO and PALBO were ultimately similar: an HR of 0.959 (0.681; 1.35) for PFS. However, following MAIC, the HR for RIBO compared with PALBO was 0.904 (0.644; 1.268). The unadjusted OS HR of 0.918 (0.517; 1.078) using PALOMA-1 improved to 0.839 (0.440; 1.598) upon exploratory MAIC. Considering comparable populations, RIBO fared better than PALBO. Although not statistically significant, these important results demonstrate that if RIBO and PALBO were compared directly, RIBO may have proved the superior agent.

When assessing therapies in breast cancer, and other diseases with relatively lengthy courses, PFS is a highly relevant outcome. PFS is measured before OS becomes apparent and provides an indication of a disease's behavior during treatment. PFS has implications for OS and may serve as a proxy for OS in the absence of complete data. MONALEESA-2 is ongoing and the limited number of OS events that have occurred to date would not be expected to accurately represent the total population. No data have been reported for PALOMA-2 OS. Both trials used PFS as the primary outcome measure and, as such, it is the most robust point of comparison for RIBO and PALBO.

In MAIC, patients in 1 population are selected according to their baseline characteristics to replicate a comparator population; this process can be said to break randomization. The implicated variables were not necessarily pre-specified as randomization variables. Simultaneously, a selection bias may result when some baseline characteristics are omitted due to availability. Of additional concern, sample size is reduced during MAIC, which can create a multiplicity bias. Finally, the addition of many variables may result in over-adjustment. Although in this analysis, the statistical fitting and testing performed indicated a moderate fit and, therefore, a limited likelihood of bias, classical and MAIC results proved relatively similar, indicating strong convergence in our findings.

The indirect comparison of RIBO with PALBO, with matching adjustment, predicted how these agents would perform under the same conditions. In our analysis, MAIC suggested 1 of 2 agents that appeared similar by ITC could be the superior choice. We demonstrate, in the absence of a head-to-head clinical trial, that RIBO could compete with or improve upon PALBO results.

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Author contributions

GT made substantial contributions to the conception and design, analyzed and interpreted the data, and critically revised the article. MD acquired and analyzed the data, and contributed to the drafting and revision of the manuscript. DC, AF, and MM made substantial contributions to conception and design, and critically revised the article for important intellectual content. JH contributed to data interpretation and drafting and revising the article. All authors agree to be accountable for all aspects of the work.

Disclosure

DC and MM are employees of Novartis. The authors report no other conflicts of interest in this work.

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