ORIGINAL RESEARCH ARTICLE

Real-World Tumor Response of Palbociclib Plus Letrozole Versus Letrozole for Metastatic Breast Cancer in US Clinical Practice

Adam Brufsky[1] · Xianchen Liu[2] · Benjamin Li[2] · Lynn McRoy[2] · Rachel M. Layman[3]

Abstract

Background Limited information exists regarding tumor response to palbociclib plus an aromatase inhibitor (AI) versus AI alone in real-world practice.

Objective To evaluate the real-world tumor response of palbociclib plus letrozole (PAL+LET) versus LET alone as first-line treatment for patients with hormone receptor-positive/human epidermal growth factor receptor 2-negative metastatic breast cancer (HR+/HER2− MBC) in routine US clinical practice.

Patients and Methods This retrospective analysis included HR+/HER2− MBC patients who initiated PAL+LET or LET as first-line treatment between February 2015 and September 2018 in the Flatiron Health Analytics database. Patients were followed until December 2018. Real-world best tumor response (rwBTR) was determined based on physicians' assessment of radiologic evidence for change in burden of disease.

Results Of the 1383 eligible patients who initiated PAL+LET or LET as first-line therapy in the Flatiron database, 968 patients had ≥ 1 tumor response assessment (662 received PAL+LET and 306 received LET). The rwBTR rate (complete response+partial response) in the first-line setting was 59.8% in the PAL+LET group and 39.2% in the LET group (odds ratio 2.31 (95% CI 1.75−3.04), $P < 0.0001$). After 1:1 propensity-score matching, the rwBTR rate was 58.6% in the PAL+LET group versus 39.1% in the LET group (odds ratio 2.21 (95% CI 1.50−3.25), $P < 0.0001$).

Conclusions This real-world analysis demonstrated that HR+/HER2− MBC patients were more likely to respond to PAL+LET compared to LET. These findings further showed the effectiveness of PAL+LET therapy in the real-world setting and support the combination as a standard of care for MBC.

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✉ Adam Brufsky
brufskyam@upmc.edu

✉ Xianchen Liu
Jasonxc.Liu@pfizer.com

1 College of Medicine, University of Pittsburgh, 300 Halket St., Suite 4628, Pittsburgh, PA 15213, USA

2 Pfizer Inc, New York, NY, USA

3 The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Key Points

This is the first comparative analysis of real-world tumor response in patients with hormone receptor-positive/human epidermal growth factor receptor 2-negative metastatic breast cancer (HR+/HER2– MBC) treated with first-line palbociclib plus letrozole versus letrozole alone in the real-world clinical setting.

Patients with HR+/HER2− MBC were more likely to respond to palbociclib plus letrozole compared with letrozole alone.

These data complement the clinical benefit of palbociclib plus endocrine therapy observed in randomized clinical trials and support palbociclib plus letrozole as a standard of care for patients with HR+/HER2− MBC.

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Plain Language Summary

Palbociclib (Ibrance®; PAL) is a treatment for advanced or metastatic breast cancer (MBC for short). Metastatic means that the cancer has spread from breast tissue to other areas of the body. PAL is taken with medications known as hormone therapy, such as letrozole (LET), to treat people with a type of MBC called hormone receptor−positive, human epidermal growth factor receptor 2–negative (HR+/HER2−). Researchers wanted to understand more about how treatment with PAL+LET affected tumor response (i.e., if the tumor shrinks or disappears) in women with HR+/HER2– MBC. We looked at tumor response to PAL+LET in a real-life setting using anonymous medical record information from a database of about 2.4 million US patients with cancer. This study included 1383 patients with HR+/HER2− MBC who started PAL+LET (754 patients) or LET alone (629 patients) as their first MBC treatment from 2015−2018. Among people who took PAL+LET, 60% people had a tumor response compared with 39% of people who took LET alone. Of the people who took PAL+LET, half of the people lived with their cancer without it getting worse for at least 20 months compared with 15 months for people who took LET alone. These results add to what is known about PAL+LET treatment based on routine clinical practice and clinical trials. Both types of information provide support for PAL+LET treatment as the standard care for women with HR+/HER2− MBC.

1 Introduction

In the USA, it was estimated that 276,480 women would be diagnosed with invasive breast cancer and 42,170 women would die from breast cancer in 2020 [1]. The majority of patients with breast cancer have hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2−) disease [2], and approximately one-third of those diagnosed with early breast cancer eventually develop metastatic disease, for which there is no cure [3, 4]. A cyclin-dependent kinase 4/6 (CDK4/6) inhibitor, such as palbociclib, in combination with endocrine therapy (ET) has been recommended as standard of care for patients with HR+/HER2− advanced or metastatic breast cancer (MBC) [5, 6].

In the PALOMA-2 clinical study, first-line palbociclib plus letrozole therapy significantly improved median progression-free survival (PFS) compared with placebo plus letrozole (27.6 vs. 14.5 months; $P < 0.0001$; data cutoff: 31 May 2017) in postmenopausal women with estrogen receptor-positive (ER+)/HER2− MBC [7]. The objective response rate (defined as confirmed complete response (CR) or partial response (PR) based on Response Evaluation Criteria in Solid Tumors (RECIST)) was 42.1% with palbociclib plus letrozole compared with 34.7% with placebo plus letrozole (odds ratio (OR), 1.40 (95% confidence interval (CI), 0.98−2.01), $P = 0.06$) [8].

Using real-world evidence to complement data from randomized controlled clinical studies is important because the stringent inclusion and exclusion criteria of oncology clinical studies exclude a substantial proportion of the patient population with cancer [9, 10]. The evaluation of multiple clinical outcomes is also important to further understand the effectiveness of treatments in the real-world setting. The various real-world endpoints have unique strengths and limitations [11, 12]. Real-world time to treatment failure is defined as the time from the start of treatment to treatment discontinuation for any reason, including death, disease progression, or adverse events [13]. However, time to treatment failure is usually not

recommended as an outcome for the regulatory approval evaluation of a new treatment because many factors may affect the time to treatment failure [13]. Real-world time to next treatment, which is defined as the time from the end of the initial treatment to the start of the next treatment, is another clinical outcome that may be evaluated, but is limited by variability in practice patterns and inaccuracy in capturing precise times of treatment initiation [12]. Real-world tumor response is evaluated based on radiologic evidence for change in disease burden throughout the course of treatment as assessed by the treating physician [14]. Real-world PFS (rwPFS) is defined as the time from the start of treatment to death or disease progression, with the treating clinician determining disease progression using radiology, pathology, laboratory findings, or clinical assessment [14]. Real-world tumor response may be assessed more reliably and objectively than rwPFS; however, there is a lack of uniformity in the timing or frequency and criteria of tumor assessment during treatment in clinical practice [12]. In addition, real-world tumor response alone may under-estimate treatment effectiveness as many patients derive benefit from prolonged stable disease [12]. Therefore, evaluation of the clinical effectiveness of a treatment utilizing multiple outcome measures is more robust and can provide a more complete understanding of treatment benefit than using any one real-world endpoint.

Findings from small and single-arm real-world studies evaluating rwPFS and OS outcomes have supported the benefit of palbociclib observed in clinical trials [15–21]. A real-world comparative effectiveness analysis using the Flatiron Health Analytics database showed that first-line palbociclib plus letrozole was more effective than letrozole alone based on median real-world PFS (20.2 vs. 11.9 months; hazard ratio, 0.54 (95% CI 0.46−0.65); $P < 0.0001$) and overall survival (OS) results (not reached vs. 43.1 months; hazard ratio 0.58 (95% CI 0.46−0.73); $P < 0.0001$) after propensity-score matching (PSM) [22]. Additionally, a recent real-world study using the Flatiron Health database evaluated tumor response to abemaciclib in 118 patients with HR+/HER2− MBC who

received abemaciclib across various lines of treatment [23]. The analysis showed that 41.2% of patients had a real-world best response (defined as real-world CR or PR).

There is limited information, however, regarding tumor response to palbociclib plus an aromatase inhibitor (AI) compared with an AI alone in real-world clinical practice [24]. A multi-country retrospective medical chart review of patients with HR+/HER2− advanced breast cancer (ABC) or MBC, who received palbociclib in combination with either an AI or fulvestrant in real-world clinical practice, reported a real-world objective response rate (based on physicians' assessments) of 79.5% in the USA and 66% in Argentina [19]. Additionally, a small real-world study of patients with HR+/HER2− ABC or MBC treated with palbociclib plus an AI or fulvestrant in Italy demonstrated a real-world objective response rate of 31% [21]. The variation in response rates observed could be attributed to differences in patient characteristics as well as the methods and criteria used to assess tumor response.

To add to the rwPFS and OS results previously reported from the Flatiron Health Analytics database [22], this retrospective analysis (using the same database) describes demographic and clinical characteristics and real-world best tumor response (rwBTR, defined as CR or PR based on the treating clinician's assessment of radiologic evidence) among a large sample of HR+/HER2− MBC patients initiating palbociclib plus letrozole compared with letrozole alone as first-line therapy in routine US clinical practice. This analysis also evaluated rwBTR rates by subgroup, including by visceral disease and bone-only metastases.

2 Methods

2.1 Study Design and Data Source

This retrospective analysis of electronic health records (EHRs) was performed using de-identified patient data from the Flatiron Health Analytics database. The Flatiron longitudinal database comprises structured and unstructured EHRs from > 280 cancer clinics and > 800 sites of care, representing approximately 2.4 million US patients with cancer who are actively being treated for their disease. Previous real-world cancer studies have demonstrated that this database has appropriate characteristics to assess treatment patterns and clinical outcomes [14, 25, 26].

2.2 Patients

Women aged ≥ 18 years with documented HR+/HER2− MBC were included in this analysis. Patients had a date of first prescription (index date) for palbociclib plus letrozole or letrozole alone as first-line therapy for MBC between 3 February 2015, and 30 September 2018, and potential follow-up for ≥ 3 months from the index date to the study cutoff date of 31 December 2018. Patients were excluded if they had prior treatment with CDK4/6 inhibitors, AIs, fulvestrant, raloxifene, tamoxifen, or toremifene in the metastatic setting; had a first structured activity > 90 days after MBC diagnostic date; or received treatment with a CDK4/6 inhibitor as part of a clinical trial.

2.3 Outcomes

The rwBTR (CR+PR), which occurred ≥ 30 days after therapy initiation, was assessed during first-line therapy using the treating clinician's assessment of radiologic evidence for change in burden of disease over the course of the treatment [14]. Unstructured physician notes and radiology reports from electronic health records were reviewed retrospectively to determine rwBTR category. CR was defined as the complete resolution of all visible disease, and PR was defined as a partial reduction in size of visible disease in some or all areas without any areas of increase in visible disease. Notably, PR should have captured a size decrease even though disease was still present. Patients with stable disease (SD) had no change in the overall size of visible disease; SD was also used for "mixed response," when patients had some lesion size increase and some lesion size decrease. Progressive disease was defined as an increase in visible disease and/or the presence of any new lesions. In situations in which the clinician explicitly stated that he or she could not make a determination of the assessment, response was classified as indeterminate.

Real-world PFS was defined as the time from the start of treatment with palbociclib plus letrozole or letrozole alone to death or disease progression. Disease progression was concluded by the treating clinician based on radiology, pathology, laboratory evidence, or clinical assessment [14]. Patients who did not die or have disease progression were censored at the date of initiation of the next line of therapy for those with two or more lines of therapy or their last visit during the study period (February 2015−December 2018) for patients with only one line of therapy.

Overall survival (OS) was defined as the time from the start of treatment with palbociclib plus letrozole or letrozole alone to death from any cause recorded by Flatiron in the data extract. The date of death was obtained from a recent mortality data set generated by combining multiple data sources and benchmarked against the National Death Index [25], which is widely considered a gold standard mortality data set in the USA [27]. Patients who did not die were censored at the time of study cutoff (31 December 2018).

2.4 Statistical Analyses

Patient characteristics and real-world best tumor response were shown using descriptive statistics. A multivariable binomial logistic regression model was used to generate propensity scores (PS) [28]. Variables used for computing PS are presented in Table 1. Individual patients in one cohort were matched 1:1 to patients in the other cohort based on closest PS using a caliper of 0.01 [28]. Logistic regression was used to estimate the odds of real-world best tumor response in the palbociclib plus letrozole group compared with the letrozole alone group. Survival time was calculated using Kaplan–Meier survival analyses. To compare the risk of rwPFS and OS between the matched study cohorts, Cox proportional hazards models with a robust sandwich estimator were used. As a sensitivity analysis, a stabilized inverse probability of treatment weighting analysis was performed.

3 Results

3.1 Study Patients

Between 3 February 2015, and 30 September 2018, 1,383 women with HR+/HER2− MBC initiated palbociclib plus letrozole ($n = 754$) or letrozole alone ($n = 629$) as first-line therapy in the Flatiron database. Among these patients, 662 patients received palbociclib plus letrozole and 306 patients received letrozole alone and had one or more tumor response assessments during first-line therapy. A total of 430 patients with one or more tumor response assessments were 1:1 PS-matched, including 215 patients who received palbociclib plus letrozole and 215 patients who received letrozole alone. After stabilized inverse probability of treatment weighting, the number of patients increased to 715 patients in the palbociclib plus letrozole group and 547 patients in the letrozole alone group.

The median duration of follow-up was 20.6 months in the palbociclib plus letrozole group and 22.3 months in the letrozole alone group. Among PS-matched patients, the median duration of follow-up was 20.2 months with palbociclib plus letrozole and 23.4 months with letrozole alone. In the stabilized inverse probability of treatment weighting cohort, the median duration of follow-up was 20.5 months in the palbociclib plus letrozole group and 20.4 in the letrozole alone group.

In the unadjusted cohort, patient demographic and clinical characteristics were different between the palbociclib plus letrozole and letrozole alone groups (Table 1). After PSM, patient characteristics were generally balanced between the matched cohorts (Table 1). After stabilized inverse probability of treatment weighting, patient characteristics were generally similar between the treatment groups (Supplemental Material, Online Resource 1).

3.2 Real-World Best Tumor Response

In the unadjusted cohort, the rwBTR rate (CR+PR) in the first-line setting was 59.8% in the palbociclib plus letrozole group and 39.2% in the letrozole alone group (OR, 2.31 (95% CI 1.75−3.04), $P < 0.0001$; Fig. 1). After PSM, the rwBTR rate was 58.6% with palbociclib plus letrozole compared with 39.1% with letrozole alone (OR, 2.21 (95% CI 1.50−3.25), $P < 0.0001$). Similarly, stabilized inverse probability of treatment weighting analysis showed a rwBTR rate of 59.3% in the palbociclib plus letrozole group and 41.5% in the letrozole alone group (OR, 2.05 (95% CI 1.64−2.57), $P < 0.0001$). An analysis of rwBTR rates by subgroups, including by visceral disease, generally showed a consistent benefit of palbociclib plus letrozole versus letrozole alone; no significant interactions were demonstrated in any of the subgroups analyzed (Fig. 2).

3.3 Real-World Progression-Free Survival and Overall Survival

Among patients with one or more tumor response assessments, treatment with palbociclib plus letrozole was associated with significantly longer ($P < 0.001$) median rwPFS versus letrozole alone in the unadjusted analysis, after PSM, and after stabilized inverse probability of treatment weighting (Fig. 3). In the unadjusted cohort, median rwPFS was 20.0 (95% CI 17.3−23.3) months with palbociclib plus letrozole and 15.1 (95% CI 12.1−18.5) months with letrozole alone (hazard ratio 0.70 (95% CI 0.58−0.84), $P = 0.0002$). After PSM, median rwPFS was 27.4 (95% CI 20.5−31.3) months in the palbociclib plus letrozole group and 15.4 (95% CI 12.1−18.5) months in the letrozole alone group (hazard ratio, 0.60 (95% CI 0.46−0.79), $P = 0.0002$). In the stabilized inverse probability of treatment weighting analysis, median rwPFS was 20.2 (95% CI 17.7−24.4) months in the palbociclib plus letrozole group and 16.9 (95% CI 12.5−21.0) months in the letrozole alone group (hazard ratio, 0.71 (95% CI 0.60−0.83), $P < 0.0001$).

Median OS was 43.4 (95% CI 33.5−not estimable [NE]) months with letrozole alone and not reached with palbociclib plus letrozole in the unadjusted analysis (hazard ratio 0.61 (95% CI 0.48−0.79), $P = 0.0001$; Fig. 4). After PSM, median OS was not reached in either the palbociclib plus letrozole or letrozole alone group (hazard ratio 0.58 (95% CI 0.39−0.85), $P = 0.0052$). In the stabilized inverse probability of treatment weighting analysis, median OS was not reached with palbociclib plus letrozole and was 43.5 (95% CI 33.5−NE) months with letrozole alone (hazard ratio 0.65 (95% CI 0.53−0.81), $P < 0.0001$).

Table 1 Patient characteristics

Characteristic	Unadjusted cohort			Cohort after PSM		
	Palbociclib + Letrozole (n = 662)	Letrozole (n = 306)	Standardized difference	Palbociclib + Letrozole (n = 215)	Letrozole (n = 215)	Standardized difference
Age, y						
Mean (SD)	64.4 (11.2)	70.6 (10.9)	0.5645	68.3 (10.8)	68.0 (10.8)	–0.0288
Median (IQR)	65.0 (57.0–73.0)	72.0 (63.0–80.0)		70.0 (62.0–76.0)	68.0 (61.0–78.0)	
Age group, n (%), y						
18–64	318 (48.0)	85 (27.8)	–0.4270	68 (31.6)	77 (35.8)	0.0886
65–74	220 (33.2)	90 (29.4)	–0.0825	81 (37.7)	76 (35.4)	–0.0483
≥ 75	124 (18.7)	131 (42.8)	0.5404	66 (30.7)	62 (28.8)	–0.0407
Race/ethnicity, n (%)						
White	462 (69.8)	216 (70.6)	0.0175	162 (75.4)	147 (68.4)	–0.1556
Black	46 (7.0)	22 (7.2)	0.0094	10 (4.7)	15 (7.0)	0.0995
Asian	15 (2.3)	6 (2.0)	–0.0212	3 (1.4)	5 (2.3)	0.0689
Hispanic or Latino	16 (2.4)	6 (2.0)	–0.0312	4 (1.9)	4 (1.9)	0.0000
Other/unknown	123 (18.6)	56 (18.3)	–0.0072	36 (16.7)	44 (20.5)	0.0957
Practice type, n (%)						
Academic	36 (5.4)	15 (4.9)	0.0242	17 (7.9)	12 (5.6)	0.0928
Community	626 (94.6)	291 (95.1)		198 (92.1)	203 (94.4)	
Disease stage at initial diagnosis, n (%)						
I or II	239 (36.1)	106 (34.6)	–0.0306	65 (30.2)	72 (33.5)	0.0699
III	92 (13.9)	45 (14.7)	0.0231	20 (9.3)	32 (14.9)	0.1718
IV	274 (41.4)	118 (38.6)	–0.0577	107 (49.8)	84 (39.1)	–0.2166
Not documented	57 (8.6)	37 (12.1)	0.1145	23 (10.7)	27 (12.6)	0.0581
ECOG performance status, n (%)						
0	278 (42.0)	72 (23.5)	–0.4013	62 (28.8)	62 (28.8)	0.0000
1	138 (20.9)	60 (19.6)	–0.0308	43 (20.0)	47 (21.9)	0.0457
2	36 (5.4)	22 (7.2)	0.0721	17 (7.9)	16 (7.4)	–0.0175
3 or 4	4 (0.6)	11 (3.6)	0.2097	3 (1.4)	2 (0.9)	–0.0434
Not documented	206 (31.1)	141 (46.1)	0.3110	90 (41.9)	88 (40.9)	–0.0189
Visceral disease,[a] n (%)						
No	378 (57.1)	210 (68.6)	–0.2403	137 (63.7)	138 (64.2)	–0.0097
Yes	284 (42.9)	96 (31.4)		78 (36.3)	77 (35.8)	
Bone-only disease,[b] n (%)	246 (37.2)	121 (39.5)	0.0490	96 (44.7)	89 (41.4)	–0.0658
Brain metastases, n (%)	16 (2.4)	14 (4.6)	0.1177	4 (1.9)	7 (3.3)	0.0885
Number of metastatic sites,[c] n (%)						
1	326 (49.2)	172 (56.2)	0.1398	127 (59.1)	123 (57.2)	–0.0377
2	193 (29.2)	71 (23.2)	–0.1357	52 (24.2)	50 (23.3)	–0.0219
3	88 (13.3)	33 (10.8)	–0.0772	25 (11.6)	27 (12.6)	0.0285
≥ 4	45 (6.8)	9 (2.9)	–0.1799	7 (3.3)	8 (3.7)	0.0254
Not documented	10 (1.5)	21 (6.9)	0.2696	4 (1.9)	7 (3.3)	0.0885

The balance in important prognostic baseline characteristics was assessed using a standardized difference approach, with a standardized difference of ≥ 0.10 considered indicative of practical significance [28]

ECOG Eastern Cooperative Oncology Group, *IQR* interquartile range, *PSM* propensity-score matching

[a]Visceral disease was defined as metastatic disease in the lung and/or liver; patients could have had other sites of metastases. No visceral disease was defined as no lung or liver metastases

[b]Bone-only disease was defined as metastatic disease in the bone only

[c]Multiple metastases at the same site were counted as one site (e.g., if a patient had three bone metastases in the spine, it was considered only one site)
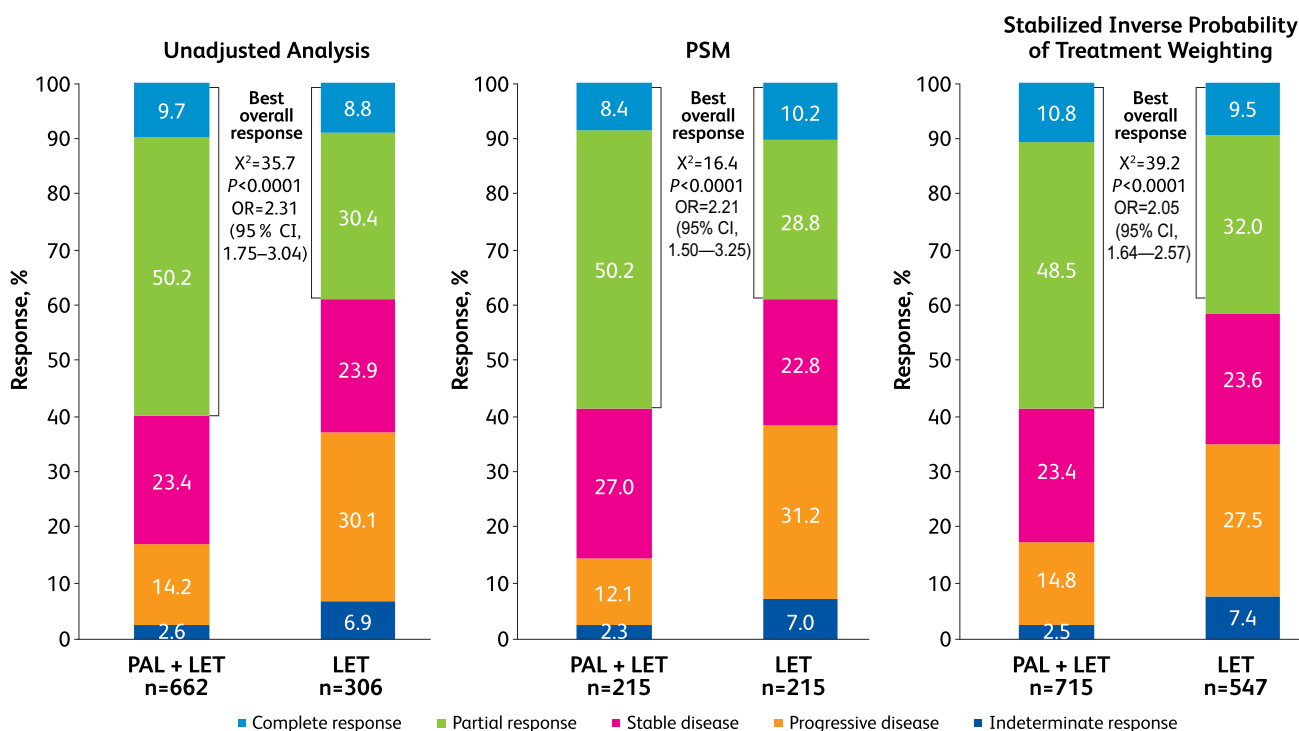
Fig. 1 Real-world best tumor response. *ECOG* Eastern Cooperative Oncology Group, *LET* letrozole, *OR* odds ratio, *PAL* palbociclib, *PSM* propensity-score matching. Indeterminate response includes sit-uations in which the clinician explicitly states that he/she is not able to make a determination of the assessment

4 Discussion

To our knowledge, this is the first comparative analysis of real-world tumor response in patients with HR+/HER2− MBC treated with first-line palbociclib plus letrozole versus letrozole alone in the real-world clinical setting. Tumor response assessments are important in clinical practice when treating patients with cancer [29]. A previous study has shown that partial or complete tumor response is associated with cancer-related symptom improvement in patients with MBC [30]. Moreover, early identification of nonresponding tumors and ineffective therapies are important to minimize the risk of disease progression and to decrease the extent of visceral disease [29].

Findings from this comparative analysis showed that patients treated in the first-line setting with palbociclib plus letrozole had an associated increased likelihood of tumor response compared with those treated with letrozole alone (after PSM, 58.6% vs. 39.1%, respectively; OR 2.21 (95% CI 1.50−3.25), *P* < 0.0001). Additionally, a generally consistent benefit of palbociclib plus letrozole versus letrozole alone was shown across subgroups, including by visceral disease and presence of bone-only metastases, with no significant interactions demonstrated in any of the subgroups evaluated. These findings complement data from randomized clinical studies showing the efficacy of palbociclib plus letrozole [7, 8, 31].

Patients included in the PALOMA-2 clinical study were postmenopausal with ER+/HER2− ABC who had not received prior systemic therapy for advanced disease [8]. Among all the randomized patients, the objective response rate was 42.1% (95% CI 37.5−46.9) with palbociclib plus letrozole and 34.7% (95% CI 28.4−41.3) with placebo plus letrozole [8]. Among patients who had measurable disease based on the Response Evaluation Criteria in Solid Tumors (RECIST) criteria, the objective response rate was 55.3% (95% CI 49.9−60.7) with palbociclib plus letrozole and 44.4% (95% CI 36.9−52.2) with placebo plus letrozole [8]. Results from this comparative analysis also demonstrated that the real-world CR rates were similar between patients treated with palbociclib plus letrozole and those who received letrozole alone (approximately 10% in both groups before and after PSM/stabilized inverse probability of treatment weighting). These results complement the CR rates reported in postmenopausal women with ER+/HER2− ABC who received first-line palbociclib plus letrozole or letrozole alone (1% in both groups) in the PALOMA-1 randomized clinical study [32] and in those who received first-line palbociclib plus letrozole or placebo plus letrozole (2.0% and 2.3%, respectively) in the PALOMA-2 randomized clinical study (data on file; Pfizer Inc, Full Clinical Study Report A5481008; 2016). The differences in CR rates observed between this present analysis and findings
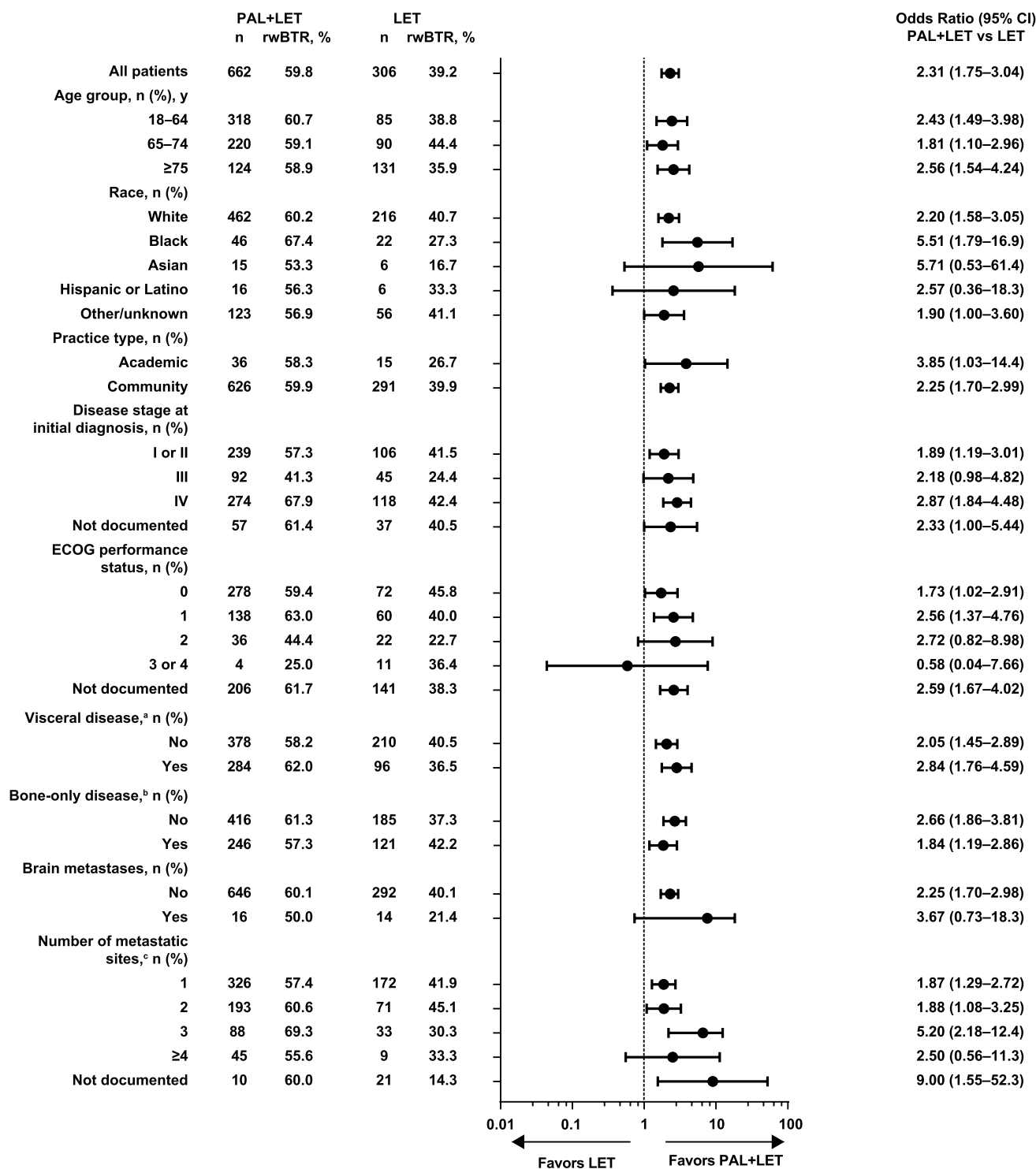
	PAL+LET		LET		Odds Ratio (95% CI) PAL+LET vs LET
	n	rwBTR, %	n	rwBTR, %	
All patients	662	59.8	306	39.2	2.31 (1.75–3.04)
Age group, n (%), y					
18–64	318	60.7	85	38.8	2.43 (1.49–3.98)
65–74	220	59.1	90	44.4	1.81 (1.10–2.96)
≥75	124	58.9	131	35.9	2.56 (1.54–4.24)
Race, n (%)					
White	462	60.2	216	40.7	2.20 (1.58–3.05)
Black	46	67.4	22	27.3	5.51 (1.79–16.9)
Asian	15	53.3	6	16.7	5.71 (0.53–61.4)
Hispanic or Latino	16	56.3	6	33.3	2.57 (0.36–18.3)
Other/unknown	123	56.9	56	41.1	1.90 (1.00–3.60)
Practice type, n (%)					
Academic	36	58.3	15	26.7	3.85 (1.03–14.4)
Community	626	59.9	291	39.9	2.25 (1.70–2.99)
Disease stage at initial diagnosis, n (%)					
I or II	239	57.3	106	41.5	1.89 (1.19–3.01)
III	92	41.3	45	24.4	2.18 (0.98–4.82)
IV	274	67.9	118	42.4	2.87 (1.84–4.48)
Not documented	57	61.4	37	40.5	2.33 (1.00–5.44)
ECOG performance status, n (%)					
0	278	59.4	72	45.8	1.73 (1.02–2.91)
1	138	63.0	60	40.0	2.56 (1.37–4.76)
2	36	44.4	22	22.7	2.72 (0.82–8.98)
3 or 4	4	25.0	11	36.4	0.58 (0.04–7.66)
Not documented	206	61.7	141	38.3	2.59 (1.67–4.02)
Visceral disease,[a] n (%)					
No	378	58.2	210	40.5	2.05 (1.45–2.89)
Yes	284	62.0	96	36.5	2.84 (1.76–4.59)
Bone-only disease,[b] n (%)					
No	416	61.3	185	37.3	2.66 (1.86–3.81)
Yes	246	57.3	121	42.2	1.84 (1.19–2.86)
Brain metastases, n (%)					
No	646	60.1	292	40.1	2.25 (1.70–2.98)
Yes	16	50.0	14	21.4	3.67 (0.73–18.3)
Number of metastatic sites,[c] n (%)					
1	326	57.4	172	41.9	1.87 (1.29–2.72)
2	193	60.6	71	45.1	1.88 (1.08–3.25)
3	88	69.3	33	30.3	5.20 (2.18–12.4)
≥4	45	55.6	9	33.3	2.50 (0.56–11.3)
Not documented	10	60.0	21	14.3	9.00 (1.55–52.3)

Favors LET ← → Favors PAL+LET

Fig. 2 Real-world best overall tumor response rates by subgroup. *ECOG* Eastern Cooperative Oncology Group, *LET* letrozole, *PAL* palbociclib, *rwBTR* real-world best tumor response [a]Visceral disease was defined as metastatic disease in the lung and/or liver; patients could have had other sites of metastases. No visceral disease was defined as no lung or liver metastases. [b]Bone-only disease was defined as metastatic disease in only the bone. [c]Multiple metastases at the same site were counted as one site (e.g., if a patient had three bone metastases in the spine, it was considered only one site)
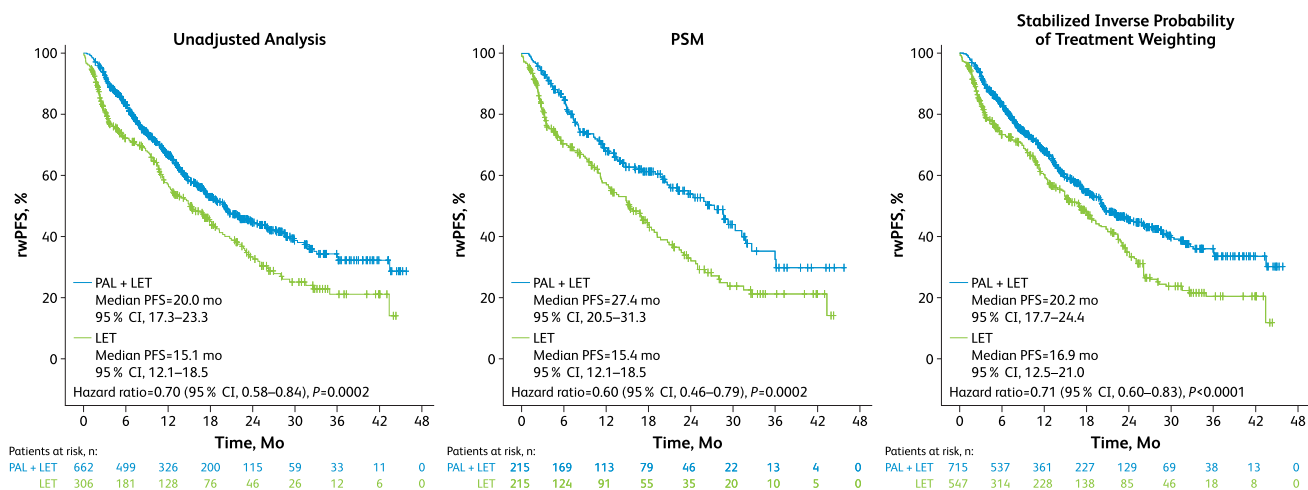
Fig. 3 Real-world progression-free survival among patients with one or more tumor response assessments. *LET* letrozole, *PAL* palbociclib, *PSM* propensity-score matching, *rwPFS* real-world progression-free survival
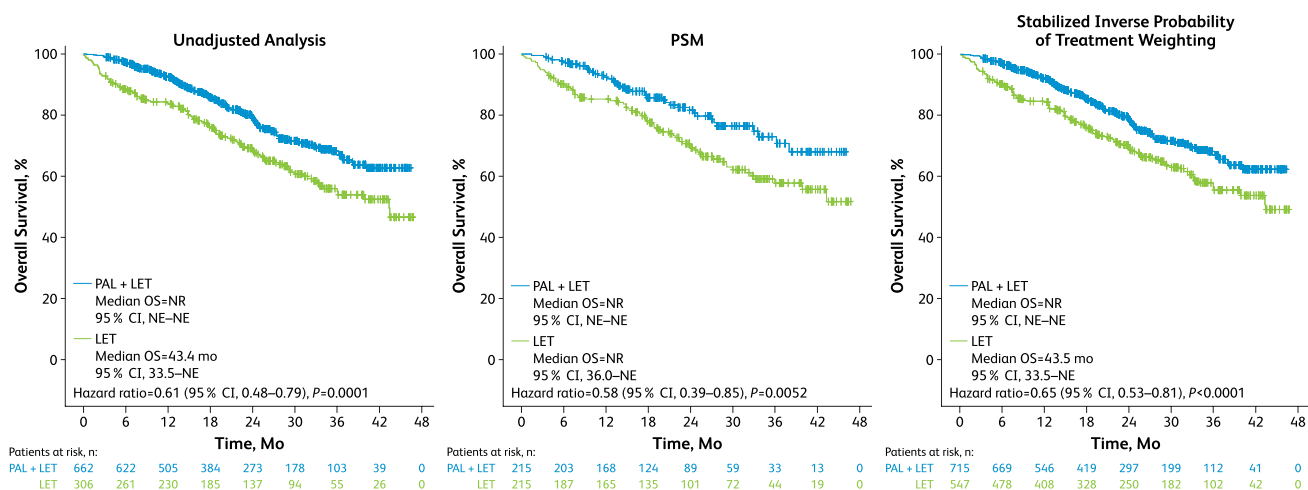

Fig. 4 Overall survival among patients with one or more tumor response assessments. *LET* letrozole, *NE* not estimable, *NR* not reached, *OS* overall survival, *PAL* palbociclib, *PSM* propensity-score matching

from the randomized clinical studies can be attributed to the differences in tumor response assessment and criteria.

The present real-world data and previous results from palbociclib clinical studies were generally similar to findings shown in randomized clinical studies of other CDK4/6 inhibitors for the treatment of women with HR+/HER2− ABC who had not received prior systemic therapy for advanced disease [32, 33]. In the MONALEESA-2 study, the objective response rate among all patients was 47% (95% CI 38−57) in the ribociclib plus letrozole group and 34% (95% CI 25−42) in the placebo plus letrozole group [32]. In patients who had measurable disease, the objective response rate was 56% (95% CI 46−66) with ribociclib plus letrozole and 45% (95% CI 34−55) with placebo plus letrozole [32]. Similarly, findings from the MONARCH 3 study reported

an objective response rate of 48.2% (95% CI 42.8−53.6) with abemaciclib plus a nonsteroidal AI and 34.5% (95% CI 27.3−41.8) with placebo plus a nonsteroidal AI [33]. In patients with measurable disease, the objective response rate was 59.2% (95% CI 53.3−65.1) in the abemaciclib group and 43.8% (95% CI 35.3−52.4) in the placebo group [33]. Together, these studies highlight the consistency of tumor response data across all CDK4/6 inhibitors, and consistent with National Comprehensive Cancer Network guidelines [5], support CDK4/6 inhibitors in combination with ET as first-line therapy for HR+/HER2− advanced/MBC.

This analysis also showed the benefit of palbociclib plus letrozole compared with letrozole alone in terms of median rwPFS and OS results. After PSM, median rwPFS was 27.4 months with palbociclib plus letrozole and 15.4 months

with letrozole alone (hazard ratio, 0.60 (95% CI 0.46−0.79), $P = 0.0002$); median OS was not reached in either the palbociclib plus letrozole or the letrozole alone group (hazard ratio, 0.58 (95% CI 0.39−0.85), $P = 0.0052$). These findings are consistent with a previous Flatiron Health real-world comparative effectiveness analysis; palbociclib plus letrozole was associated with longer median rwPFS and OS compared with letrozole alone (20.2 vs. 11.9 months and not reached vs. 43.1 months, respectively, both $P < 0.0001$) [22]. These results also complement the results from the PALOMA-2 clinical study, which reported a median PFS of 27.6 months with palbociclib plus letrozole versus 14.5 months with placebo plus letrozole ($P < 0.0001$; data cutoff: 31 May 2017) [7]. OS data from PALOMA-2 have not been reported yet.

The present findings should be interpreted in the context of the following limitations. First, this is a retrospective analysis of data from an EHR database and causal relationships to treatment cannot be determined. Second, similar to other EHR databases, the Flatiron Health database may have missing or erroneous data, including data that may not be missing at random [34]. Tumor response assessments were missing in a higher proportion of patients treated with letrozole alone compared with those treated with palbociclib plus letrozole. Third, tumor assessments in routine practice were not scheduled and were not confirmed by additional imaging. These data were limited by the clinician's interpretation and documentation of tumor response based on radiologic evidence for change in burden of disease, and tumor response assessment was not based on RECIST. Fourth, although PSM was used to balance patient characteristics and stabilized inverse probability of treatment weighting was used as a sensitivity analysis, other variables unavailable in the database, such as menopausal status, disease-free interval, and endocrine sensitivity could not be statistically controlled. Additionally, tolerability and adverse events data were not collected in the database and were not evaluated in this analysis. Moreover, these findings may not be generalizable to other patient populations.

Despite these limitations, the real-world tumor response findings and associated response benefit shown in patients treated with palbociclib plus letrozole are supported by the observed rwPFS and OS benefit. In addition, results from the stabilized inverse probability of treatment weighting sensitivity analysis were consistent with findings from the PSM analysis. Moreover, the real-world tumor response variable is less likely to be confounded by comorbid conditions, unobserved variables, or subsequent treatments that may affect PFS or OS. Although further real-world studies are needed, these findings add to the current body of evidence supporting the effectiveness of palbociclib combination therapy in the first-line setting, complementing the results from randomized clinical studies and other evidence of effectiveness endpoints. Real-world studies provide valuable insights into the benefits of palbociclib in a general oncology population of patients with HR+/HER2− ABC/MBC treated in routine clinical practice, including those with demographic and disease characteristics that may not be represented in randomized clinical trials.

5 Conclusion

Patients with HR+/HER2− MBC treated with first-line palbociclib plus letrozole were associated with a significantly higher likelihood of tumor response than those treated with letrozole alone in this large cohort of general oncology practice patients in the USA. In addition, treatment with first-line palbociclib plus letrozole was associated with significant rwPFS and OS improvement compared with letrozole alone. These data complement the clinical benefit observed with palbociclib plus endocrine therapy in randomized clinical trials and support palbociclib plus letrozole as a standard of care for patients with HR+/HER2− MBC.

months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer. The data on the real-world cohort that support the findings of this study have been originated by Flatiron Health, Inc and were purchased by Pfizer from Flatiron Health Inc for the purpose of this research. Access to the de-identified data set is subject to a contractual agreement with Flatiron Health; for data access, interested researchers should contact DataAccess@flatiron.com. A licensing agreement is legally required prior to sharing these data in order to safeguard sensitive patient information, and to ensure proper deidentification and compliance with applicable restrictions and requirements under HIPAA.

Code availability Not applicable.

Author contributions All authors contributed to the conception and design of the study, provided study materials, data interpretation and analysis, drafted the manuscript, and/or critically revised the manuscript for intellectual contribution. BL collected and assembled data. All authors approved the final version of the manuscript for submission.

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