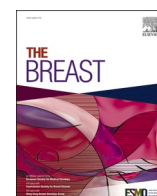




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Real-world effectiveness of palbociclib in combination with an aromatase inhibitor in HR+/HER2– bone-only metastatic breast cancer

Adam Brufsky^{a,*}, Rachel M. Layman^b, Xianchen Liu^c, Benjamin Li^d, Lynn McRoy^c, Aaron B. Cohen^e, Melissa Estevez^e, Paul Cottu^f, Giuseppe Curigliano^{g,h}, Hope S. Rugoⁱ

^a Division of Hematology/Oncology, Department of Medicine, UPMC Hillman Cancer Center, University of Pittsburgh Medical Center, Pittsburgh, PA, USA

^b Department of Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

^c US Oncology Medical Affairs, Pfizer Inc, New York, NY, USA

^d Global Biometrics & Data Management, Pfizer Inc, New York, NY, USA

^e Flatiron Health Inc., New York, NY, USA

^f Department of Medical Oncology & Institute of Women Cancers, Institut Curie, Université Paris Cité, Paris, France

^g Department of Oncology and Hemato-Oncology, University of Milano, Milano, Italy

^h European Institute of Oncology (IEO) IRCCS, Milano, Italy

ⁱ Breast Medical Oncology, City of Hope Comprehensive Cancer Center, Duarte, CA, USA

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ABSTRACT

Background: Cyclin-dependent kinase (CDK) 4/6 inhibitors plus endocrine therapy (ET) are more effective than ET alone in diverse populations of patients with HR+/HER2– metastatic breast cancer (MBC). However, real-world effectiveness data for CDK4/6 inhibitors plus ET combination in bone-only MBC are limited.

Methods: This retrospective, real-world study compared clinical outcomes of first-line (1L) palbociclib (PAL) plus an aromatase inhibitor (AI) with AI alone in bone-only MBC using data from the US-based, nationwide Flatiron Health Research database. Eligible patients had HR+/HER2– bone-only MBC, were ≥18 years of age, and started 1L PAL + AI or AI alone from February 2015 to June 2022. Stabilized inverse probability of treatment weighting (sIPTW) was used to balance baseline characteristics. Overall survival (OS), real-world progression-free survival (rwPFS), and time to chemotherapy (TTC) were evaluated.

Results: Of 974 eligible patients with bone-only MBC, 538 received PAL + AI and 436 received AI alone. After sIPTW, baseline patient characteristics were balanced between treatment groups. Median follow-up was 31.9 months for the PAL + AI group and 35.8 months for the AI group. After sIPTW, the PAL + AI group compared with the AI group had a significantly longer OS (median 63.4 vs 51.3 months; HR = 0.78; 95% CI, 0.64–0.97, $P = 0.0221$), rwPFS (median 23.0 vs 18.2 months; HR = 0.72; 95% CI, 0.59–0.87, $P = 0.0008$), and TTC (median 47.9 vs 40.6 months; HR = 0.79; 95% CI, 0.66–0.96, $P = 0.016$). Consistent results were observed in unadjusted and sensitivity analyses.

Conclusion: This real-world study demonstrates that first-line PAL + AI versus AI alone was associated with prolonged OS, rwPFS, and TTC in patients with HR+/HER2– bone-only MBC.

Trial registration number: NCT06495164.

1. Introduction

Palbociclib, an oral cyclin-dependent kinase 4/6 (CDK4/6) inhibitor, in combination with endocrine therapy (ET), was approved for the treatment of hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2–) advanced/metastatic breast

cancer (MBC) in 2015 [1]. Two additional CDK4/6 inhibitors, ribociclib and abemaciclib, were approved in 2017 [2,3]. A CDK4/6 inhibitor with ET has become the standard of care for first-line (1L) treatment of patients with HR+/HER2– MBC [4,5]. In addition to randomized controlled trials (RCTs), which have shown the efficacy of CDK4/6 inhibitors plus ET in HR+/HER2– MBC, real-world studies have also

* Corresponding author. Division of Hematology/Oncology, Department of Medicine UPMC Hillman Cancer Center University of Pittsburgh Medical Center 1218 Scaife Hall 3550 Terrace Street Pittsburgh, PA, 15261, USA.

E-mail address: brufskyam@upmc.edu (A. Brufsky).

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demonstrated the effectiveness of CDK4/6 inhibitors plus ET versus ET alone in diverse patient populations with MBC, including older patients, African American patients, patients with visceral metastases, and patients with cardiovascular comorbidities [6–11]. However, some patients who are eligible for combination therapy, including those with bone-only metastases, are often still treated with ET alone [12].

Studies have reported that as many as 80% of patients with de novo and recurrent MBC have distant metastases to bone [13–16]. Bone is the most frequent site of metastasis in patients with HR+/HER2– MBC with spread to a single site [17], particularly in de novo MBC [18]. Historically, patients with bone-only MBC have been considered to have relatively lower disease burden, with better clinical outcomes than those with metastasis to other sites [19–21]. As such, patients with bone-only MBC may be viewed as candidates for ET monotherapy [15,22]. Despite bone-only MBC having better outcomes than MBC with spread to other sites, bone-only MBC remains incurable and has a 5-year survival rate of 43.5% [23]. Furthermore, patients with bone-only metastases may experience reduced quality of life compared with those without bone

metastases [24,25]. There is a clear need for the development and application of new therapies for this large patient population.

Evidence from RCTs indicates that patients with bone-only disease may benefit from CDK4/6 inhibitor plus ET combination therapy [26, 27]. Subgroup analyses from the PALOMA-2, MONALEESA-2, and MONARCH 3 trials showed that progression-free survival (PFS) and overall survival (OS) were numerically longer in the CDK4/6 inhibitor plus ET arms than in the placebo plus ET arms, with palbociclib plus letrozole and abemaciclib plus an aromatase inhibitor (AI) resulting in significantly prolonged PFS and OS, respectively [28–33]. However, sample sizes of bone-only subgroups were generally small in these studies ($n < 150$ per arm). In other clinical trials, patients with bone-only disease have frequently been included in nonvisceral disease subgroups, complicating interpretation of the results [27,34]. Real-world data can supplement findings from RCTs to investigate whether patients with bone-only metastases have benefited from CDK4/6 inhibitors in everyday clinical practice. To date, evidence of the real-world effectiveness of CDK4/6 inhibitors in the bone-only

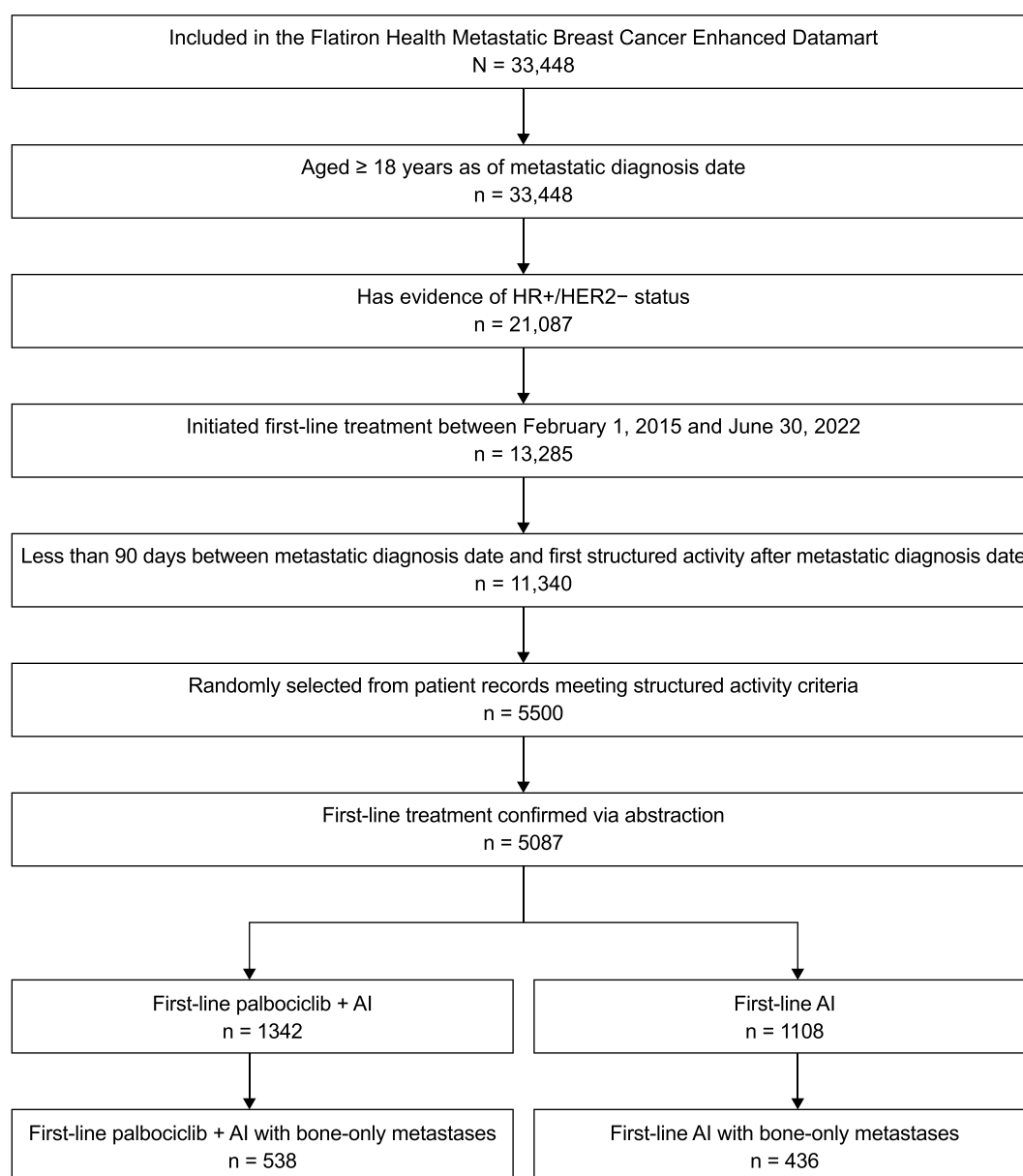


Fig. 1. Patient attrition diagram.

AI, aromatase inhibitor; HR+/HER2–, hormone receptor-positive/human epidermal growth factor receptor 2-negative.

population is limited. One subgroup analysis of patients with bone-only metastases from a large United States (US) database has shown that extended real-world progression-free survival (rwPFS) and longer OS were associated with palbociclib plus ET compared with ET alone [9]. However, the subgroup analysis was exploratory and did not adjust for baseline characteristics when comparing clinical outcomes. To help fill these knowledge gaps, the current study compared OS, rwPFS, and time to chemotherapy (TTC) of 1L palbociclib plus an AI versus an AI alone in HR+/HER2 bone-only MBC in US routine clinical practice.

2. Methods

2.1. Study design and data source

This was a retrospective, observational study of patient data obtained from the Flatiron Health Enhanced MBC Datamart (N = 33,448 at data cutoff of December 2022). The Flatiron Health database contains deidentified patient-level structured and unstructured data collected from ~280 cancer clinics (~800 sites of care), representing more than 3 million actively treated patients with cancer in the US. Records for patients aged ≥ 18 years with HR+/HER2- MBC who initiated 1L treatment between February 2015 and June 2022 and who had structured activity less than 90 days after their metastatic diagnosis date were randomly sampled (n = 5500). From this sample, 5087 patients had 1L treatment data manually confirmed via abstraction (Fig. 1). Patients who initiated 1L palbociclib plus an AI or 1L AI alone during the index period and who had bone-only disease were included in the study.

2.2. Outcomes

The outcomes assessed included OS, rwPFS, and TTC. OS was defined as the number of months from palbociclib plus AI or AI initiation until the date of death [9,35]. Three data sources were used to determine the date of death: Social Security Death Index (SSDI), obituary data, and electronic health records-derived mortality data that was previously validated against the National Death Index (NDI) [36,37]. rwPFS was defined as the number of months from palbociclib plus AI or AI initiation until death or disease progression as determined by clinical assessment or radiographic scan/biopsy [9,35]. TTC was defined as the number of months from palbociclib plus AI or AI initiation until the start of subsequent chemotherapy or death from any cause. If patients had not started chemotherapy or had died, they were censored at last medical activity or end of the study, whichever came first [38].

2.3. Statistical analysis

Patient demographics and baseline disease characteristics were summarized using descriptive statistics. For time-to-event endpoints, median survival times were calculated using the Kaplan–Meier method, and survival plots were generated. The weighted Cox proportional hazards model was used to compute hazard ratios (HRs) and corresponding 95% confidence intervals (CIs). Stabilized inverse probability of treatment weight (sIPTW) was the primary analysis and was used to balance baseline patient demographics and clinical characteristics. A sensitivity analysis was conducted using 1:1 propensity score matching (PSM). Propensity scores were calculated using a multivariable logistic regression model and served as the basis for both sIPTW and PSM analyses. Variables included in the model were age group, sex, race and ethnicity, practice type, disease stage at initial diagnosis, Eastern Cooperative Oncology Group (ECOG) performance status, interval from initial breast cancer diagnosis to MBC diagnosis, and number of metastatic sites [9]. Baseline characteristic balance was determined by calculating standardized mean differences, with values ≥ 0.1 indicating a non-negligible imbalance. All data analyses were performed using statistical software SAS version 9.4 or later.

3. Results

3.1. Patients

Of 5087 patients with confirmed 1L treatment for their HR+/HER2- MBC, 1342 started treatment with palbociclib plus an AI and 1108 started treatment with an AI alone between February 1, 2015 and June 30, 2022 (Fig. 1). Of patients receiving palbociclib plus an AI, 538 had bone-only disease, and of patients receiving an AI alone, 436 had bone-only disease. The proportions of patients with estrogen receptor-positive (ER+) only, progesterone receptor-positive (PR+) only, and both ER+ and PR + MBC were 22.2%, 0.7%, and 77.1% in the palbociclib plus AI group and 26.9%, 0.7%, and 72.4% in the AI-alone group, with no significant difference between groups ($\chi^2 = 2.88$, $P > 0.05$). Median follow-up was 31.9 months in the palbociclib plus AI group and 35.8 months in the AI-alone group. Baseline patient demographics and disease characteristics are shown in Table 1. Overall, most patients in the palbociclib + AI and AI-alone groups were treated in community practices (76.6% and 83.5%, respectively). Patients in the palbociclib plus AI group were younger than those in the AI-alone group (median age 66 vs 71 years), had a higher proportion of patients with de novo MBC (44.6% vs 35.8%), and ECOG performance status 0 (35.1% vs 25.5%). Following sIPTW and PSM, baseline patient demographics and disease characteristics were well balanced between the two treatment groups.

3.2. Overall survival

Kaplan–Meier curves of OS are shown in Fig. 2. In the unadjusted analysis, patients receiving palbociclib plus an AI had significantly longer OS than those receiving an AI alone (median 67.7 months [95% CI, 57.2–83.1] versus 48.0 months [95% CI, 40.9–55.0]; HR = 0.66 [95% CI, 0.55–0.81], $P < 0.0001$). After sIPTW (primary analysis), palbociclib plus AI was associated with significantly longer OS compared with an AI alone (median 63.4 months [95% CI, 56.2–79.6] vs 51.3 months [95% CI, 44.8–65.1]), resulting in a significant reduction in the risk of death of 22% (HR = 0.78 [95% CI, 0.64–0.97], $P = 0.0221$). In the PSM sensitivity analysis, OS was numerically longer in patients treated with palbociclib plus an AI than an AI alone (median 63.4 months [95% CI, 56.7–83.1] vs 49.8 months [95% CI, 42.5–63.6]). Similarly, palbociclib plus an AI versus an AI alone had > 20% risk reduction in mortality albeit the reduction was not statistically significant (HR = 0.77 [95% CI, 0.60–1.00], $P = 0.0530$).

3.3. Real-world progression-free survival

Kaplan–Meier curves of rwPFS are shown in Fig. 3. In the unadjusted analysis, patients treated with palbociclib plus an AI had significantly longer rwPFS than those treated with an AI alone (median 24.8 months [95% CI, 21.7–28.8] vs 18.1 months [95% CI, 13.8–20.3]; HR = 0.66 [95% CI, 0.55–0.79], $P < 0.0001$). Following sIPTW, patients in the palbociclib plus AI group had a median rwPFS of 23.0 months (95% CI, 20.7–26.7), compared with 18.2 months (95% CI, 13.3–20.9) in the AI-alone group; the risk of disease progression or death was significantly reduced by 28% (HR = 0.72 [95% CI, 0.59–0.87], $P = 0.0008$). The results were similar following the PSM sensitivity analysis, with the rwPFS being significantly longer in the palbociclib plus AI group (median 24.1 months [95% CI, 20.5–26.7]) than in the AI-alone group (median 20.1 months [95% CI, 16.0–23.3]; HR = 0.74 [95% CI, 0.59–0.94], $P = 0.0148$).

3.4. Time to chemotherapy

Kaplan–Meier curves of TTC are shown in Fig. 4. In the unadjusted analysis, TTC was significantly extended in patients receiving palbociclib plus an AI compared with those receiving an AI alone (median 49.5 months [95% CI, 42.2–56.0] vs 38.7 months [95% CI, 33.3–43.5]; HR =

Table 1
Patient demographics and disease characteristics at baseline.

Characteristic	Unadjusted analysis			sIPTW analysis			PSM analysis		
	PAL + AI (n = 538)	AI alone (n = 436)	Std difference	PAL + AI (n = 537)	AI alone (n = 435)	Std difference	PAL + AI (n = 282)	AI alone (n = 282)	Std difference
Age at MBC diagnosis, years									
Mean (SD)	64.8 (11.6)	70.1 (10.9)	−0.4785	66.9 (11.5)	67.7 (11.4)	−0.0705	67.9 (10.9)	68.8 (10.9)	−0.0811
Median (IQR)	66 (15)	71 (16)	—	68 (17)	69 (17)	—	69 (16)	70 (17)	—
Age group,^a n (%)									
18–49 years	55 (10.2)	20 (4.6)	0.2165	41 (7.6)	31 (7.1)	0.0177	11 (3.9)	14 (5.0)	−0.0517
50–64 years	196 (36.4)	108 (24.8)	0.2551	168 (31.3)	136 (31.3)	0.0007	80 (28.4)	79 (28.0)	0.0079
65–74 years	168 (31.2)	129 (29.6)	0.0356	164 (30.6)	134 (30.9)	−0.0052	101 (35.8)	98 (34.8)	0.0223
≥75 years	119 (22.1)	179 (41.1)	−0.4161	164 (30.5)	134 (30.7)	−0.0055	90 (31.9)	91 (32.3)	−0.0076
Sex,^a n (%)									
Male	5 (0.9)	8 (1.8)	−0.0776	7 (1.3)	6 (1.4)	−0.0058	3 (1.1)	1 (0.4)	0.0846
Female	533 (99.1)	428 (98.2)	—	530 (98.7)	429 (98.6)	—	279 (98.9)	281 (99.6)	—
Race and ethnicity,^a n (%)									
White	374 (69.5)	293 (67.2)	0.0498	367 (68.3)	297 (68.2)	0.0026	213 (75.5)	197 (69.9)	0.1276
Black	43 (8.0)	45 (10.3)	−0.0808	48 (9.0)	40 (9.1)	−0.0047	18 (6.4)	21 (7.4)	−0.0419
Other ^b	121 (22.5)	98 (22.5)	0.0003	122 (22.7)	99 (22.7)	0.0003	51 (18.1)	64 (22.7)	−0.1146
Practice type,^a n (%)									
Academic	126 (23.4)	72 (16.5)	0.1734	113 (21.0)	92 (21.2)	−0.0053	60 (21.3)	49 (17.4)	0.0989
Community	412 (76.6)	364 (83.5)	—	424 (79.0)	343 (78.8)	—	222 (78.7)	233 (82.6)	—
Insurance, n (%)									
Commercial health plan + any other	182 (33.8)	163 (37.4)	−0.0743	193 (36.0)	155 (35.6)	0.0081	101 (35.8)	98 (34.8)	0.0223
Commercial health plan	193 (35.9)	123 (28.2)	0.1648	180 (33.6)	127 (29.3)	0.0935	96 (34.0)	80 (28.4)	0.1227
Medicare	28 (5.2)	31 (7.1)	−0.0793	29 (5.4)	31 (7.1)	−0.0704	17 (6.0)	22 (7.8)	−0.0699
Medicaid	6 (1.1)	6 (1.4)	−0.0235	5 (1.0)	6 (1.3)	−0.0319	1 (0.4)	5 (1.8)	−0.1386
Other payer type	129 (24.0)	113 (25.9)	−0.0448	129 (24.0)	116 (26.7)	−0.0618	67 (23.8)	77 (27.3)	−0.0814
Disease stage at initial diagnosis,^a n (%)									
I	60 (11.2)	66 (15.1)	−0.1181	74 (13.7)	61 (14.1)	−0.0104	33 (11.7)	38 (13.5)	−0.0535
II	131 (24.3)	108 (24.8)	−0.0098	129 (24.1)	102 (23.5)	0.0135	78 (27.7)	65 (23.0)	0.1061
III	75 (13.9)	68 (15.6)	−0.0467	79 (14.6)	65 (15.0)	−0.0097	46 (16.3)	37 (13.1)	0.0902
IV	240 (44.6)	156 (35.8)	0.1808	216 (40.3)	175 (40.1)	0.0040	103 (36.5)	120 (42.6)	−0.1235
Not documented	32 (5.9)	38 (8.7)	−0.1063	39 (7.2)	32 (7.3)	−0.0025	22 (7.8)	22 (7.8)	0.0000
ECOG performance status,^a n (%)									
0	189 (35.1)	111 (25.5)	0.2116	166 (31.0)	134 (30.9)	0.0022	91 (32.3)	87 (30.9)	0.0305
1	132 (24.5)	98 (22.5)	0.0486	129 (24.0)	104 (23.9)	0.0030	58 (20.6)	66 (23.4)	−0.0685
≥2	67 (12.5)	70 (16.1)	−0.1032	73 (13.7)	60 (13.8)	−0.0041	39 (13.8)	35 (12.4)	0.0420
Not documented	150 (27.9)	157 (36.0)	−0.1750	168 (31.3)	137 (31.4)	−0.0018	94 (33.3)	94 (33.3)	0.0000
No. of metastatic sites,^{a,c} n (%)									
1	518 (96.3)	416 (95.4)	0.0436	516 (96.2)	419 (96.2)	0.0005	271 (96.1)	274 (97.2)	−0.0590
2	20 (3.7)	20 (4.6)	—	20 (3.8)	17 (3.8)	—	11 (3.9)	8 (2.8)	—
≥3	0	0	—	0	0	—	0	0	—
Not documented	0	0	—	0	0	—	0	0	—
Disease-free interval in years,^{a,d} n (%)									
De novo	240 (44.6)	156 (35.8)	0.1808	216 (40.3)	175 (40.1)	0.0040	103 (36.5)	120 (42.6)	−0.1235
≤1	26 (4.8)	23 (5.3)	−0.0202	29 (5.4)	23 (5.4)	−0.0002	14 (5.0)	16 (5.7)	−0.0316
>1 to 5	83 (15.4)	105 (24.1)	−0.2187	103 (19.2)	86 (19.7)	−0.0117	53 (18.8)	51 (18.1)	0.0183
>5	189 (35.1)	150 (34.4)	0.0153	188 (35.1)	151 (34.6)	0.0100	112 (39.7)	95 (33.7)	0.1253
Not documented	0	2 (0.5)	−0.0960	0	1 (0.2)	−0.0642	0	0	—
NCI Comorbidity Index									
Mean (SD)	0.31 (0.5)	0.41 (0.6)	−0.2002	0.33 (0.5)	0.38 (0.6)	−0.0984	0.34 (0.5)	0.36 (0.6)	−0.0538
Follow-up duration, months									
Median (IQR)	31.9 (33.5)	35.8 (43.4)	—	30.2 (33.6)	38.2 (46.3)	—	30.0 (33.8)	38.0 (44.1)	—

AI, aromatase inhibitor; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; MBC, metastatic breast cancer; NCI, National Cancer Institute; No., number; PAL, palbociclib; PSM, propensity score matching; SD, standard deviation; sIPTW, stabilized inverse probability of treatment weighting; std, standardized.

^a Variable used in propensity score estimation.

^b Other also includes Asian, Hispanic or Latino.

^c Multiple metastases at the same site were counted as 1 site (eg, if a patient had 3 bone metastases in the spine, it was considered only 1 site).

^d Defined as the interval from initial breast cancer diagnosis to MBC diagnosis.

0.73 [95% CI, 0.61–0.87], $P = 0.0004$). After sIPTW, median TTC was 47.9 months (95% CI, 41.1–56.0) with palbociclib plus an AI compared with 40.6 months (95% CI, 35.5–47.2) with an AI alone. As a result, the risk of subsequent chemotherapy was significantly reduced by 21% (HR = 0.79 [95% CI, 0.66–0.96], $P = 0.016$). In the PSM sensitivity analysis, TTC was numerically longer in the palbociclib plus AI group (median 49.5 months [95% CI, 42.1–58.2]) than in the AI-alone group (median 41.8 months [95% CI, 35.8–47.6]), although the difference was not statistically significant (HR = 0.81 [95% CI, 0.64–1.02], $P = 0.0764$).

4. Discussion

Bone is the most common site of distant metastasis in HR+/HER2– MBC [17]. When patients have metastatic tumors that are restricted to bone, the disease is characterized by relatively favorable survival outcomes compared with other metastatic sites [21,39]. Despite the high prevalence of bone-only MBC, it has received less research attention compared with other metastatic sites. To our knowledge, this is the first real-world comparative study evaluating the effectiveness of a CDK4/6 inhibitor with an AI versus an AI alone in bone-only MBC. In this analysis, 1L treatment of patients with HR+/HER2– bone-only MBC

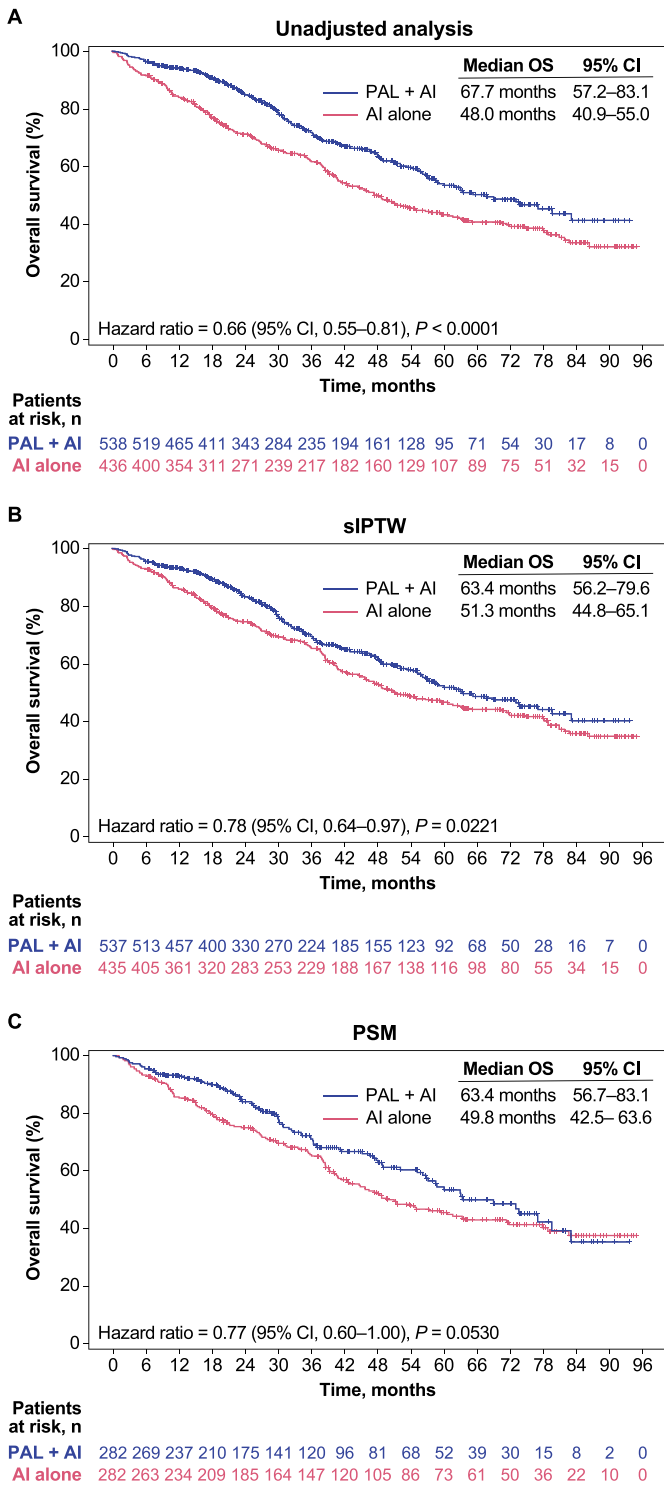


Fig. 2. Plots of Kaplan–Meier estimates for overall survival. AI, aromatase inhibitor; CI, confidence interval; HR, hazard ratio; PAL, palbociclib; OS, overall survival, PSM, propensity score matching; sIPTW, stabilized inverse probability of treatment weighting.

with palbociclib combined with an AI was associated with a statistically significant benefit in OS, rwPFS, and TTC relative to an AI alone (following sIPTW, all HR < 0.80; $P < 0.05$).

Previous data on CDK4/6 inhibitor efficacy for patients with bone-only MBC primarily originates from subgroup analyses of RCTs. In the PALOMA-2 trial, a subgroup of patients with bone-only disease ($n = 151$) taking palbociclib plus letrozole had a numerically better median

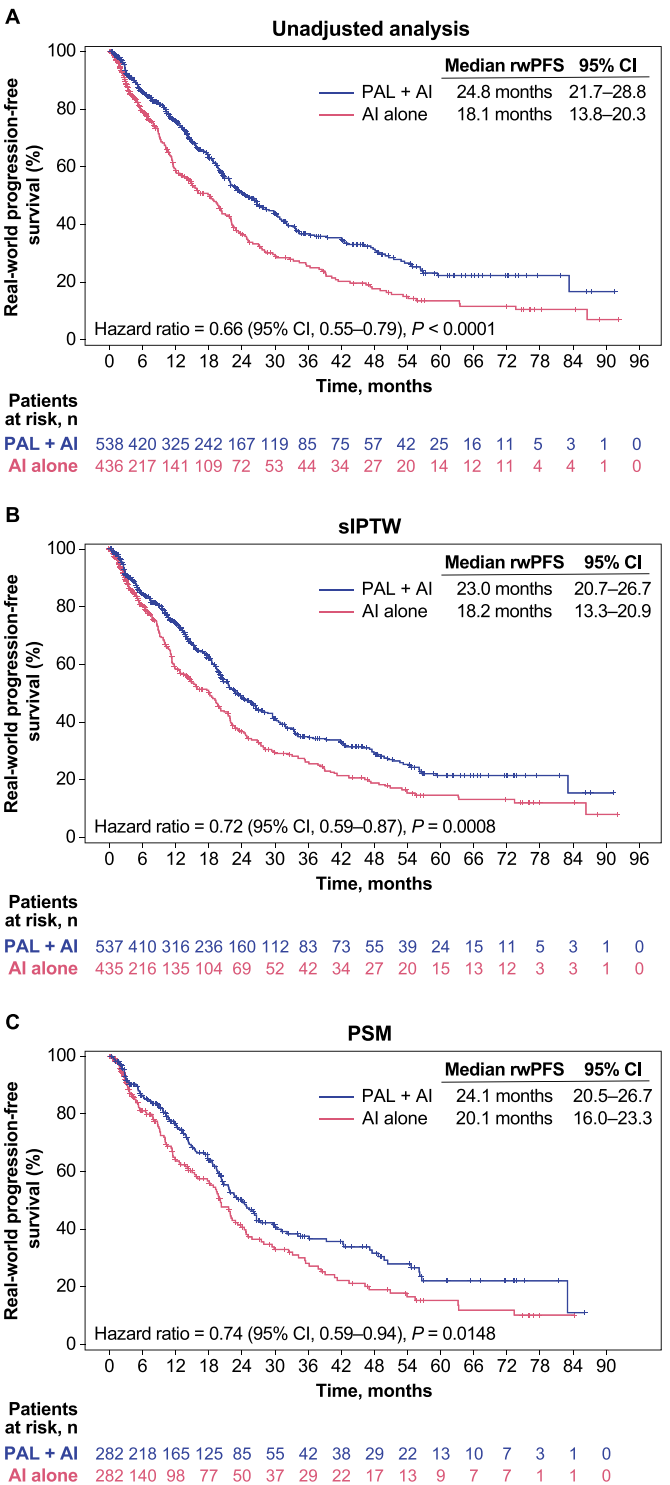


Fig. 3. Plots of Kaplan–Meier estimates for real-world progression-free survival. AI, aromatase inhibitor; CI, confidence interval; HR, hazard ratio; PAL, palbociclib; PSM, propensity score matching; rwPFS, real-world progression-free survival; sIPTW, stabilized inverse probability of treatment weighting.

OS (63.5 months [95% CI, 53.9–79.7]) than those taking placebo plus letrozole (52.3 months [95% CI, 42.3–59.7]; HR = 0.71 [95% CI, 0.46–1.10]) [33]. Furthermore, median PFS was significantly better with palbociclib plus letrozole (36.2 months [95% CI, 27.6–not estimable]) than with placebo plus letrozole (11.2 months [95% CI, 8.2–22.0]; HR = 0.40 [95% CI, 0.26–0.62]) [28,40]. In the

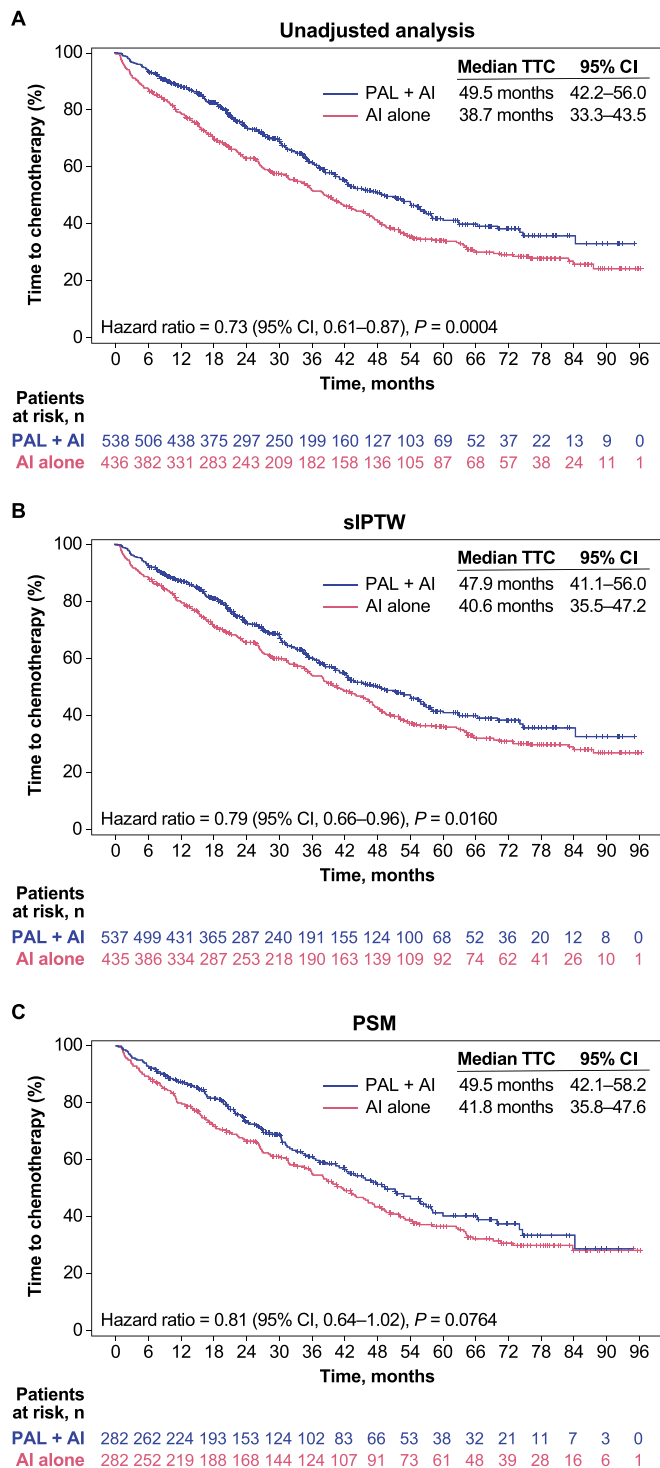


Fig. 4. Plots of Kaplan–Meier estimates for time to chemotherapy. AI, aromatase inhibitor; CI, confidence interval; HR, hazard ratio; PAL, palbociclib; PSM, propensity score matching; sIPTW, stabilized inverse probability of treatment weighting; TTC, time to chemotherapy.

MONALEESA-2 trial, patients in the bone-only subgroup (*n* = 148) receiving ribociclib plus letrozole versus placebo plus letrozole had numerically longer median OS (HR = 0.78 [95% CI, 0.50–1.21]) and median PFS (HR = 0.69 [95% CI, 0.38–1.25]) [31,32]. In the MONARCH 3 trial, patients in the bone-only subgroup (*n* = 109) receiving abemaciclib plus a nonsteroidal AI showed statistically significantly prolonged OS compared with placebo plus a nonsteroidal AI (HR = 0.60 [95% CI, 0.36–0.99]), while PFS was numerically longer (HR = 0.58 [95% CI,

0.27–1.25]) [29,30]. A meta-analysis of bone-only MBC subgroups in RCTs (PALOMA-2, MONARCH 3, MONALEESA-2, and MONALEESA-7) reported a collective PFS advantage of the experimental arms over the control arms but noted that only PALOMA-2 (palbociclib plus letrozole compared with placebo plus letrozole) demonstrated a PFS improvement that was statistically significant [27]. Although care should be taken in comparing findings from RCTs with real-world studies, the efficacy results from subgroup analyses of bone-only patients in RCTs are broadly consistent with the OS and rwPFS benefits of palbociclib combined with an AI observed in this analysis.

Real-world evidence can supplement findings from RCTs in support of treatment decision-making, in part through the analysis of diverse patient subgroups [41,42]. Most real-world data on CDK4/6 inhibitor effectiveness have been generated for palbociclib, which has now been approved for over a decade [1,43]. A subgroup analysis of patients with bone-only MBC (*n* = 531) from a large scale study using the Flatiron Health database showed a reduced risk of death and disease progression for those treated with palbociclib plus letrozole versus letrozole alone (HR = 0.72 [95% CI, 0.53–0.97] and HR = 0.55 [95% CI, 0.45–0.68], respectively) [35]. Similar results were observed in a subsequent, larger study (*n* = 1118) using records from the Flatiron Health database, which showed OS and rwPFS benefits for those treated with palbociclib plus an AI versus an AI alone (HR = 0.77 [95% CI, 0.62–0.95] and HR = 0.74 [95% CI, 0.62–0.88], respectively) [9]. The addition of palbociclib to letrozole has also been associated with better real-world best tumor response rate than letrozole alone (*n* = 367; 57.3% vs 42.2%; odds ratio = 1.84 [95% CI, 1.19–2.86]) [44]. However, the majority of existing subgroup analyses had small numbers of patients, relatively short follow-ups, and did not adjust for baseline demographic and clinical characteristics when comparing outcomes between patients with bone-only MBC treated with CDK4/6 inhibitors plus ET versus ET alone. In contrast, the current study balanced baseline characteristics using sIPTW in the primary analysis and PSM in the sensitivity analysis. Furthermore, this study assessed 3 clinical outcomes, OS, rwPFS, and TTC, to determine the effectiveness of palbociclib plus AI versus an AI alone. Given the difficulty and variability associated with assessing bone disease progression [45,46], TTC, a chart abstraction-independent endpoint [47], is an important supplement to rwPFS and is especially clinically meaningful to patients, as prolonged TTC is associated with preservation of quality of life [48,49]. The effectiveness observed in this study in OS, rwPFS, and TTC from both primary and sensitivity analyses, together with prior subgroup analyses, suggests significant clinical benefits for patients with bone-only MBC treated with palbociclib plus an AI compared with an AI alone.

Although head-to-head RCTs comparing the approved CDK4/6 inhibitors have not been conducted, real-world data on their relative effectiveness in a US patient population have been recently published. Pairwise comparison of OS for patients with bone-only MBC taking palbociclib (*n* = 3171), ribociclib (*n* = 591), and abemaciclib (*n* = 481) did not find any statistically significant differences in risk of death [50]. A similar analysis of rwPFS among the 3 approved CDK4/6 inhibitors also found no significant differences in outcomes for patients with bone-only MBC [Rugo, 2025, submitted]. Other real-world comparison studies have generally not included bone-only subgroups; therefore, additional real-world evidence, including data for international patient groups, is needed. Because these CDK4/6 inhibitors appear to exhibit similar effectiveness for HR+/HER2– MBC with bone-only involvement, treatment selection may be based on their unique safety profiles and individual patient characteristics.

This study has some limitations. Since this is a retrospective observational study, only associations, and not causality, between treatments and outcomes can be inferred. As with any retrospective database analyses, it may have incomplete, missing, or inaccurate data. Disease progression was not evaluated according to a predefined schedule, nor were standardized clinical trial assessments used. As a result, rwPFS data

relied on the treating physician's interpretation of pathology reports and scan results. Assessing bone-only MBC disease progression is difficult, contributing to inter-investigator variability; lesions associated with bone remodeling may be present, and flares associated with treatment response may be mistaken for disease progression using some radiographic modalities [34,45,46]. Variables included in the dataset are limited; details salient to the population of patients with MBC and bone-only metastases, such as the occurrence of pathological fractures, bone pain, reduced mobility and functional decline, were not available for this study. Treatment selection bias may have been introduced because treatments were not randomly assigned. Instead, treatments were selected based on the treating physician's clinical judgment and may have been impacted by disease characteristics, such as histological grade and/or sensitivity to ET that were not captured in the dataset used for this study. Treatment decision-making may also have been impacted by the fact that bone-only disease is known to be generally less aggressive. Even though sIPTW and PSM were used to balance patient characteristics between treatment groups, the effect of unmeasured potential confounders, such as the use of bone-modifying agents, could not be adjusted for in these analyses. Finally, the Flatiron Health database is limited to practices in the network in the US, and hence these results may not be generalizable outside of this network. Despite these limitations, our study has a number of key strengths. The relatively large dataset drawn from the diverse, nationwide Flatiron Health database permits the evaluation of a patient population that has been previously assessed only in subgroup and post hoc analyses. The general agreement between the primary analysis (sIPTW) and sensitivity analysis (PSM) supports the robustness of the findings. Finally, the findings of the 3 clinical outcomes—including OS, rwPFS, and TTC rather than 1 single outcome—are consistent, supporting the benefit of palbociclib plus an AI versus an AI alone in bone-only MBC.

5. Conclusion

First-line palbociclib plus an AI versus an AI alone was significantly associated with prolonged OS, rwPFS, and TTC in patients with HR+/HER2– bone-only MBC in routine US clinical practice. These findings support the use of 1L palbociclib in combination with ET for HR+/HER2– bone-only MBC.

CRedit authorship contribution statement

Adam Brufsky: Writing – review & editing, Conceptualization. **Rachel M. Layman:** Writing – review & editing, Conceptualization. **Xianchen Liu:** Writing – review & editing, Formal analysis, Conceptualization. **Benjamin Li:** Writing – review & editing, Formal analysis, Conceptualization. **Lynn McRoy:** Writing – review & editing, Conceptualization. **Aaron B. Cohen:** Writing – review & editing, Conceptualization. **Melissa Estevez:** Writing – review & editing, Conceptualization. **Paul Cottu:** Writing – review & editing, Conceptualization. **Giuseppe Curigliano:** Writing – review & editing, Conceptualization. **Hope S. Rugo:** Writing – review & editing, Conceptualization. All authors read and approved the final manuscript.

Ethics statement

This retrospective database analysis was conducted in accordance with the Guidelines for Good Pharmacoepidemiology Practice, Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research, and Good Practices for Real-World Data Studies of Treatment and/or Comparative Effectiveness. As this study was retrospective and noninterventional and used anonymized data, it was exempt from institutional review board approval and included a waiver of informed consent.

Declaration of competing interest

Adam Brufsky has received grants from Agendia and AstraZeneca; consulting fees or honoraria from AstraZeneca, Pfizer, Novartis, Eli Lilly, Genentech/Roche, Seagen, Daiichi-Sankyo, Merck, Agendia, Sanofi, and Puma.

Rachel M. Layman has received advisory/consultancy fees from Novartis, Eli Lilly, Gilead Sciences, Biotheryx, and Celcuity; honorarium provided by Pfizer; institutional research support from Pfizer Inc, Novartis, Eli Lilly, Puma, Celcuity, Accutar Biotech, Arvinas, and Biotheryx.

Xianchen Liu, Benjamin Li, and Lynn McRoy are employees of and stockholders in Pfizer Inc.

Aaron B. Cohen and Melissa Estevez are employees of Flatiron Health and are stockholders in Roche.

Paul Cottu has received honoraria for consulting or advisory roles from Novartis and Pfizer; research funding from AstraZeneca, Genentech/Roche, Novartis, Pierre Fabre, and Pfizer; reimbursement for travel, accommodations, or expenses from AstraZeneca, NanoString Technologies, Novartis, Pfizer, and Roche.

Giuseppe Curigliano has received honoraria from Ellipses Pharma; consulting or advisory role for Genentech/Roche, Pfizer, Novartis, Eli Lilly, Foundation Medicine, Bristol Myers Squibb, Samsung, AstraZeneca, Daiichi-Sankyo, Boehringer Ingelheim, GlaxoSmithKline, Seagen, Guardant Health, Veracyte, Celcuity, Hengrui Therapeutics, Menarini, and Merck; speakers' bureau for Genentech/Roche, Novartis, Pfizer, Eli Lilly, Foundation Medicine, Samsung, Daiichi-Sankyo, Seagen, and Menarini; research funding from Merck (Inst); and travel, accommodations, and expenses from Genentech/Roche, Pfizer, and Daiichi-Sankyo.

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Glossary

AI	aromatase inhibitor
CDK	cyclin-dependent kinase
ECOG	Eastern Cooperative Oncology Group
ET	endocrine therapy
HER+/HER2–	hormone receptor-positive/human epidermal growth factor receptor 2-negative
MBC	metastatic breast cancer
NCI	National Cancer Institute
OS	overall survival
PAL	palbociclib
rwPFS	real-world progression-free survival
TTC	time to chemotherapy

Data availability

Upon request, and subject to review, Pfizer will provide the data that

support the findings of this study. Subject to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual deidentified participant data. See <https://www.pfizer.com/science/clinical-trials/trial-data-and-results> for more information.

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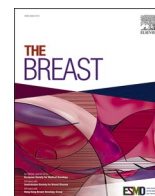
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Update

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Corrigendum

Corrigendum to “Real-world effectiveness of palbociclib in combination with an aromatase inhibitor in HR+/HER2– bone-only metastatic breast cancer” [The Breast 86 (2026) 104744]

Adam Brufsky^{a,*}, Rachel M. Layman^b, Xianchen Liu^c, Benjamin Li^d, Lynn McRoy^c, Aaron B. Cohen^e, Melissa Estevez^e, Paul Cottu^f, Giuseppe Curigliano^{g,h}, Hope S. Rugoⁱ

^a Division of Hematology/Oncology, Department of Medicine, UPMC Hillman Cancer Center, University of Pittsburgh Medical Center, Pittsburgh, PA, USA

^b Department of Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

^c US Oncology Medical Affairs, Pfizer Inc, New York, NY, USA

^d Global Biometrics & Data Management, Pfizer Inc, New York, NY, USA

^e Flatiron Health Inc., New York, NY, USA

^f Department of Medical Oncology & Institute of Women Cancers, Institut Curie, Université Paris Cité, Paris, France

^g Department of Oncology and Hemato-Oncology, University of Milano, Milano, Italy

^h European Institute of Oncology (IEO) IRCCS, Milano, Italy

ⁱ Breast Medical Oncology, City of Hope Comprehensive Cancer Center, Duarte, CA, USA

The authors regret a small mistake in the methods section. This mistake does not impact the results, descriptions and conclusions of the work but is important enough to require correction. We sincerely apologize for any inconvenience caused.

Corrigendum Section 2.2: The last sentence ‘If patients had not

started chemotherapy or had died, they were censored at last medical activity or end of the study, whichever came first [38].’ was corrected to ‘If patients had not started chemotherapy and were alive, they were censored at last medical activity or end of the study, whichever came first [38].’.

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* Corresponding author. Division of Hematology/Oncology, Department of Medicine, UPMC Hillman Cancer Center University of Pittsburgh Medical Center, 1218, Scaife Hall 3550 Terrace Street, Pittsburgh, 15261, PA, USA.

E-mail address: brufskyam@upmc.edu (A. Brufsky).

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