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Real-world overall survival with palbociclib plus an aromatase inhibitor in overweight/obese patients with HR+/HER2– metastatic breast cancer

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Objective

To compare overall survival (OS), time to subsequent chemotherapy (TSC), and subsequent treatment patterns in overweight/obese patients who received palbociclib plus an aromatase inhibitor (AI) or an AI alone as first-line (1L) treatment for their hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2–) metastatic breast cancer (MBC) in US routine clinical practice.

Conclusions

- Compared with an AI alone, palbociclib plus an AI was associated with improved OS in overweight/obese patients with HR+/HER2– MBC in the US real-world setting.
- Compared with an AI alone, palbociclib plus an AI was associated with prolonged TSC in overweight/obese patients with HR+/HER2– MBC.
- Although a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i)-containing therapy was the most common subsequent therapy for both treatment groups, patients who started 1L AI alone were more likely to receive a subsequent CDK4/6i-containing therapy than those who started palbociclib plus an AI.
- These findings support 1L palbociclib plus an AI as a standard of care (SOC) for overweight/obese patients with HR+/HER2– MBC.

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Background

- A CDK4/6i combined with endocrine therapy (ET) has been the SOC as 1L treatment for HR+/HER2– MBC for the past decade.[1]
- Palbociclib, the first CDK4/6i approved, received accelerated US approval in 2015 for HR+/HER2– MBC based on its demonstrated efficacy and safety profile.[2]
- An increasing number of real-world studies have shown that 1L palbociclib plus ET significantly improves progression-free survival, tumor response, and OS compared with ET alone across diverse HR+/HER2– MBC populations.[3,4]
- Overweight and obesity are common conditions associated with an increased risk of breast cancer and can influence cancer treatment outcomes.[5,6]
- However, little is known about the effectiveness of palbociclib plus ET in overweight/obese patients with HR+/HER2– MBC in routine US clinical practice.

Methods

STUDY DESIGN AND DATA SOURCE

- This was a retrospective analysis of deidentified longitudinal patient data from the US nationwide Flatiron Health Database.
- The Flatiron Health Database contains patient-level structured and unstructured data, originating from ~280 cancer clinics (~800 sites of care), representing >3 million actively treated patients with cancer in the US.
- Patients who were overweight or obese (BMI ≥25 kg/m^2), had HR+/HER2– MBC, and initiated 1L palbociclib plus an AI or an AI alone between February 2015 and July 2024 (index period) were included in the study.

OUTCOMES

- OS was defined as the number of months from start of index palbociclib plus AI or AI alone to death from any cause.
- Date of death was a consensus mortality endpoint based on electronic health records, the Social Security Death Index, and obituary data, validated against the National Death Index.[7]
- TSC was defined as the length of time from the start of index treatment to the beginning of subsequent chemotherapy (CT) or death from any cause, whichever came first.

STATISTICAL ANALYSIS

- Baseline demographics and disease characteristics were summarized by descriptive statistics.
- Stabilized inverse probability of treatment weighting (sIPTW, primary analysis) was used to balance baseline patient demographics and clinical characteristics, and 1:1 propensity score matching (PSM) was performed as a sensitivity analysis.
- Survival times for time-to-event endpoints were calculated using the Kaplan–Meier method.
- The weighted Cox proportional hazards model was used to compute hazard ratios (HRs) and corresponding 95% confidence intervals (CIs).

Results

PATIENTS

- A total of 8076 patients were eligible for analysis, including 5009 (62.0%) treated with palbociclib + AI and 3067 (38.0%) treated with an AI alone.
- The arithmetic median duration of follow-up was 32.8 months for the palbociclib + AI group versus 24.5 months for the AI alone group (**Table 1**).
- Compared with the AI alone group, the palbociclib + AI group was younger (median age 66.0 vs 71.0 years) and had a lower proportion of patients with ECOG PS 2–4 (12.6% vs 17.8%; **Table 1**). However, the palbociclib + AI group had a higher proportion of patients with ≥2 metastatic sites (29.9% vs 22.0%) and lung and/or liver involvement (33.3% vs 26.6%) than in the AI alone group.
- After sIPTW, baseline patient demographics and clinical characteristics were generally well balanced between the treatment groups (**Table 1**).

Table 1. Baseline patient demographics and disease characteristics

	Unadjusted			sIPTW		
Characteristic	1L PAL + AI n = 5009	1L AI alone n = 3067	Standardized difference[a]	1L PAL + AI n = 5005	1L AI alone n = 3070	Standardized difference[a]
Age at MBC diagnosis,[a] years						
Mean (SD)	65.4 (11.2)	69.8 (11.2)	−0.3891	66.8 (11.2)	67.2 (11.5)	−0.0384
Median (IQR)	66 (16)	71 (16)	–	68 (17)	68 (16)	–
Age group, n (%)						
18–49	452 (9.0)	162 (5.3)	0.1456	381 (7.6)	236 (7.7)	−0.0024
50–64	1753 (35.0)	748 (24.4)	0.2338	1554 (31.0)	952 (31.0)	0.0006
65–74	1644 (32.8)	945 (30.8)	0.0431	1610 (32.2)	985 (32.1)	0.0016
75+	1160 (23.2)	1212 (39.5)	−0.3583	1460 (29.2)	897 (29.2)	−0.0009
Sex,[a] n (%)						
Female	4939 (98.6)	3040 (99.1)	−0.0488	4943 (98.8)	3031 (98.7)	0.0046
Male	70 (1.4)	27 (0.9)	–	61 (1.2)	39 (1.3)	–
Race,[a] n (%)						
White	3165 (63.2)	1975 (64.4)	−0.0252	3183 (63.6)	1948 (63.5)	0.0030
Black	550 (11.0)	311 (10.1)	0.0273	532 (10.6)	329 (10.7)	−0.0028
Other	1294 (25.8)	781 (25.5)	0.0084	1289 (25.8)	793 (25.8)	−0.0014
Practice type, n (%)						
Academic	786 (15.7)	493 (16.1)	−0.0105	799 (16.0)	491 (16.0)	−0.0003
Community	4223 (84.3)	2574 (83.9)	–	4205 (84.0)	2579 (84.0)	–
Insurance, n (%)						
Commercial health plan + any other	1636 (32.7)	1013 (33.0)	−0.0078	1689 (33.7)	950 (31.0)	0.0596
Commercial health plan	1570 (31.3)	878 (28.6)	0.0593	1520 (30.4)	930 (30.3)	0.0017
Medicaid	80 (1.6)	44 (1.4)	0.0133	74 (1.5)	50 (1.6)	−0.0139
Medicare	275 (5.5)	232 (7.6)	−0.0841	292 (5.8)	206 (6.7)	−0.0361
Other payer type	1448 (28.9)	900 (29.3)	−0.0096	1430 (28.6)	933 (30.4)	−0.0399
Disease stage at initial diagnosis, n (%)						
Stage I	503 (10.0)	330 (10.8)	−0.0235	511 (10.2)	311 (10.1)	0.0025
Stage II	1062 (21.2)	587 (19.1)	0.0514	1030 (20.6)	642 (20.9)	−0.0079
Stage III	520 (10.4)	317 (10.3)	0.0015	534 (10.7)	335 (10.9)	−0.0076
Stage IV	2691 (53.7)	1654 (53.9)	−0.0041	2670 (53.4)	1623 (52.9)	0.0100
Not documented	233 (4.7)	179 (5.8)	−0.0532	260 (5.2)	160 (5.2)	−0.0011
ECOG performance status,[a] n (%)						
0	1660 (33.1)	737 (24.0)	0.2027	1496 (29.9)	916 (29.8)	0.0010
1	1459 (29.1)	746 (24.3)	0.1087	1365 (27.3)	841 (27.4)	−0.0027
2–4	633 (12.6)	546 (17.8)	−0.1442	725 (14.5)	446 (14.5)	−0.0017
Not documented	1257 (25.1)	1038 (33.8)	−0.1928	1420 (28.4)	867 (28.2)	0.0030
Visceral metastasis,[b] n (%)						
Yes	1668 (33.3)	817 (26.6)	0.1458	1546 (30.9)	953 (31.0)	−0.0030
No	3341 (66.7)	2250 (73.4)	–	3459 (69.1)	2118 (69.0)	–
Bone-only metastases, n (%)						
Yes	2461 (49.1)	1394 (45.5)	0.0738	2386 (47.7)	1460 (47.6)	0.0020
No	2548 (50.9)	1673 (54.5)	–	2619 (52.3)	1610 (52.4)	–
No. of metastatic sites,[a,c] n (%)						
1	3071 (61.3)	1775 (57.9)	0.0701	3005 (60.0)	1841 (59.9)	0.0019
2	1102 (22.0)	518 (16.9)	0.1294	1004 (20.1)	612 (19.9)	0.0031
≥3	397 (7.9)	156 (5.1)	0.1153	343 (6.9)	215 (7.0)	−0.0056
Not documented	439 (8.8)	618 (20.1)	−0.3281	652 (13.0)	402 (13.1)	−0.0021
Disease-free interval in years,[a,d] n (%)						
De novo	2691 (53.7)	1654 (53.9)	−0.0041	2670 (53.4)	1623 (52.9)	0.0100
≤1	217 (4.3)	135 (4.4)	−0.0034	221 (4.4)	136 (4.4)	−0.0003
>1–5	764 (15.3)	460 (15.0)	0.0071	766 (15.3)	485 (15.8)	−0.0130
>5	1337 (26.7)	818 (26.7)	0.0005	1347 (26.9)	827 (27.0)	−0.0006
Median follow-up duration						
Months (IQR)	32.8 (34.2)	24.5 (35.8)	–	32.5 (33.9)	25.0 (36.4)	–

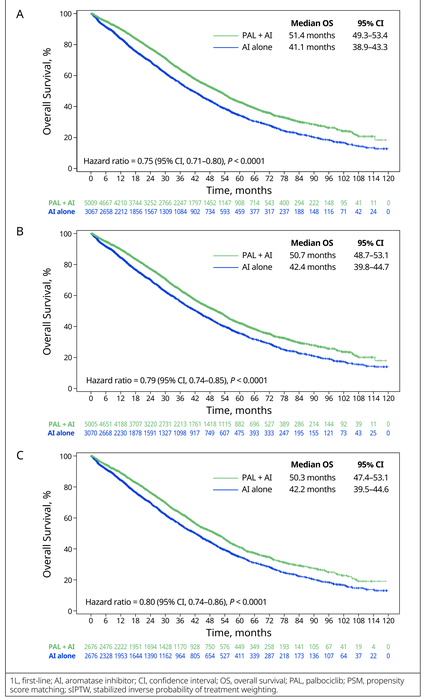
[a]Variable used in propensity score estimation; [b]Visceral metastasis was defined as metastatic disease in the lung and/or liver; [c]Multiple metastases at the same site were counted as 1 site (eg, if a patient had 3 bone metastases in the spine, it was considered only 1 site); [d]Defined as the interval from initial breast cancer diagnosis to MBC diagnosis. ªThe balance in these baseline characteristics was assessed using a standardized mean differences approach, with values ≥0.1 indicating a non-negligible imbalance.

1L, first-line; AI, aromatase inhibitor; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; MBC, metastatic breast cancer; PAL, palbociclib; SD, standard deviation; sIPTW, stabilized inverse probability of treatment weighting.

OVERALL SURVIVAL

- 1L palbociclib + AI was significantly associated with prolonged OS compared with an AI alone:
  - In the unadjusted analysis (**Figure 1A**), median OS was 51.4 months (95% CI, 49.3–53.4) versus 41.1 months (95% CI, 38.9–43.3); HR = 0.75 (95% CI, 0.71–0.80), $P < 0.0001$.
  - After sIPTW (**Figure 1B**), median OS was 50.7 months (95% CI, 48.7–53.1) versus 42.4 months (95% CI, 39.8–44.7); HR = 0.79 (95% CI, 0.74–0.85), $P < 0.0001$.
  - Following PSM sensitivity analysis (**Figure 1C**), median OS was 50.3 months (95% CI, 47.4–53.1) versus 42.2 months (95% CI, 39.5–44.6); HR = 0.80 (95% CI, 0.74–0.86), $P < 0.0001$.

Figure 1. Comparison of OS between palbociclib plus AI and an AI alone as 1L treatment for overweight/obese patients in the unadjusted analysis (A), after sIPTW (B), and after PSM (C).

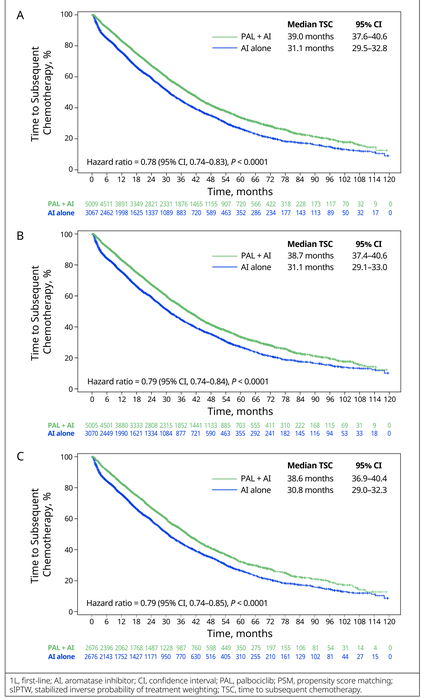


1L, first-line; AI, aromatase inhibitor; CI, confidence interval; OS, overall survival; PAL, palbociclib; PSM, propensity score matching; sIPTW, stabilized inverse probability of treatment weighting.

TIME TO SUBSEQUENT CHEMOTHERAPY

- Patients who received 1L palbociclib + AI had a significantly longer TSC than those who received an AI alone:
  - In the unadjusted analysis (**Figure 2A**), median TSC was 39.0 months (95% CI, 37.6–40.6) versus 31.1 months (95% CI, 29.5–32.8); HR = 0.78 (95% CI, 0.74–0.83), $P < 0.0001$.
  - After sIPTW (**Figure 2B**), median TSC was 38.7 months (95% CI, 37.4–40.6) versus 31.1 months (95% CI, 29.1–33.0); HR = 0.79 (95% CI, 0.74–0.84), $P < 0.0001$.
  - Following PSM (**Figure 2C**), median TSC was 38.6 months (95% CI, 36.9–40.4) versus 30.8 months (95% CI, 29.0–32.3); HR = 0.79 (95% CI, 0.74–0.85), $P < 0.0001$.

Figure 2. Comparison of TSC between palbociclib plus AI and an AI alone as 1L treatment for overweight/obese patients in the unadjusted analysis (A), after sIPTW (B), and after PSM (C).

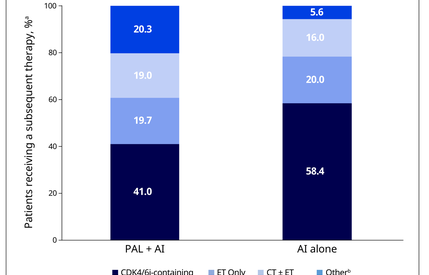


1L, first-line; AI, aromatase inhibitor; CI, confidence interval; PAL, palbociclib; PSM, propensity score matching; sIPTW, stabilized inverse probability of treatment weighting; TSC, time to subsequent chemotherapy.

SUBSEQUENT TREATMENTS

- After sIPTW, 51.2% of patients received a 2L treatment after palbociclib + AI and 58.8% received a 2L treatment following an AI alone during a median follow-up of 32.5 and 25.0 months, respectively.
- Among patients who received a 2L treatment after 1L palbociclib + AI, 41.0% received a CDK4/6i-containing regimen, 19.7% received ET alone, 19.0% received CT with/without ET, and 20.3% received other therapies (**Figure 3**).
- Among patients who received a 2L treatment after an AI alone, 58.4% received a CDK4/6i-containing regimen, 20.0% received ET alone, 16.0% received CT with/without ET, and 5.6% received other therapies (**Figure 3**).

Figure 3. Subsequent treatments in overweight/obese patients and who received 1L palbociclib plus AI or an AI alone after sIPTW



[a]Percentage of patients who received subsequent treatment (defined as a change in systemic therapy triggering a line advancement except for changes in AI).

[b]Key other therapies included ESR1-targeted therapies, everolimus, HER2-targeted therapies, PARPi-based therapies, PIK3CA-targeted therapies, and therapies targeting VEGF.

1L, first-line; AI, aromatase inhibitor; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CT, chemotherapy; ESR1, estrogen receptor alpha; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; PAL, palbociclib; PARPi, poly (ADP-ribose) polymerase inhibitors; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha; sIPTW, stabilized inverse probability of treatment weighting; VEGF, vascular endothelial growth factor.

LIMITATIONS

- This was a retrospective, observational design study; as such, only associations between treatments and outcomes can be inferred rather than causality.
- Treatments were selected for each patient based on the treating physician's clinical judgement and experience rather than randomization.
- Overweight/obese was defined based on BMI, which does not reflect body composition metrics such as muscle mass and fat distribution.
- It was possible that database entries may have been incomplete, missing, or inaccurate.
- sIPTW and PSM were used to balance patient characteristics between treatment groups, but the effect of unmeasured potential confounders such as comorbidities and concomitant medications could not be adjusted for in these analyses.
- Since this analysis was based on data collected in the US, the results may not be generalizable to other patient populations.

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