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Concomitant Proton Pump Inhibitor Use and Clinical Outcomes with Palbociclib or Abemaciclib in Metastatic Breast Cancer: A Multicenter Retrospective Study

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Abstract

Proton pump inhibitors (PPIs) diminish the absorption levels of multiple oncology agents. The potential influence of PPIs when administered alongside cyclin-dependent kinase 4/6 inhibitors remains under debate. This investigation sought to establish if concurrent PPI administration alters the therapeutic benefits of palbociclib and abemaciclib in managing breast cancer. A retrospective observational analysis was performed across multiple centers involving 4 healthcare facilities in Japan. Eligible participants were sequentially recruited individuals diagnosed with hormone therapy-resistant advanced breast cancer who initiated treatment with either palbociclib or abemaciclib from December 2017 through August 2022. Matching based on propensity scores was implemented. Clinical outcomes and tolerability profiles were evaluated between cohorts with and without PPI exposure. Kaplan-Meier estimates were generated for progression-free and overall survival, with differences assessed via log-rank testing. Hazard ratios were derived from Cox regression modeling. Overall, 240 cases were analyzed. Following 1:1 propensity matching, 112 subjects remained in each arm. The median duration of progression-free survival stood at 1.2 years among PPI recipients versus 1.3 years in those avoiding PPIs (hazard ratio, 1.19; 95% CI, 0.70-2.02). Overall survival reached a median of 3.6 years in the PPI arm, while it remained undetermined in the comparator arm (hazard ratio, 1.23; 95% CI, 0.61-2.47). Comparable patterns emerged in unmapped cohorts treated with palbociclib (n = 177) or abemaciclib (n = 63). Toxicity profiles, including frequency and intensity, showed no notable differences across arms. Concurrent administration of PPIs does not appear to compromise the clinical performance of cyclin-dependent kinase 4/6 inhibitors. Additional forward-looking investigations focused on pharmacokinetics are advised.

Keywords: Breast cancer, Palbociclib, Abemaciclib, Proton pump inhibitor, Propensity score

Introduction

Breast cancer (BC) stands as the predominant malignancy and the fourth primary contributor to oncology-related mortality among females, registering nearly 2.3 million diagnoses worldwide in 2020 [1]. Within Japan, close to 97,000 incidents of BC occurred in 2019 [2]. Projections indicate that 1 out of every 9 women in Japan will encounter BC over their lifespan. Advanced breast cancer (mBC) offers no curative options for affected individuals. Roughly 60% of such advanced cases classify as luminal type, featuring positive hormone receptors alongside negative human epidermal growth factor receptor 2 (HER2) status [3].

Integrating cyclin-dependent kinase 4/6 (CDK4/6) inhibitors—including palbociclib, ribociclib, and abemaciclib—with hormonal treatments like aromatase blockers or estrogen antagonists substantially improves progression-free survival over solitary hormonal approaches in hormone receptor-positive, HER2-negative advanced disease [4-9]. Guidelines now endorse this paired strategy as the benchmark initial or subsequent therapy for premenopausal and postmenopausal cases of this molecular profile [10, 11]. Distinct from typical cytotoxic regimens, CDK4/6

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inhibitors impede cell cycle advancement from G1 into S phase, thereby curbing DNA production and tumor expansion [12]. In the Japanese setting, both oral palbociclib and abemaciclib have secured recent authorization for hormone receptor-positive, HER2-negative advanced BC. In contrast, ribociclib lacks approval, primarily owing to heightened hepatotoxicity concerns observed in local populations [13].

Concurrent administration of proton pump inhibitors (PPIs) markedly shortens progression-free survival among individuals with metastatic breast cancer undergoing therapy with palbociclib or ribociclib [14-16]. A likely explanation for such drug interactions involves increased gastric pH induced by PPIs, which impairs dissolution and subsequent uptake of various antineoplastic agents [17-20]. In contrast, multiple investigations have failed to demonstrate any significant interaction [21-24]. Consequently, the clinical relevance of combining PPIs with CDK4/6 inhibitors continues to be disputed. Prior research predominantly employed retrospective observational approaches and focused on cases of hormone receptor-positive, HER2-negative metastatic breast cancer. Nevertheless, many of these analyses omitted details regarding treatment sequence, inclusion requirements, or patient responsiveness to hormonal interventions. Reported progression-free survival in endocrine-responsive cases treated with palbociclib reached 24.8 months, compared to merely 9.5 months in those exhibiting resistance [4, 5]. Given that outcomes from these distinct populations cannot be directly compared, the current analysis targeted exclusively endocrine-resistant individuals who had not received prior chemotherapy. This choice was made because overall survival in endocrine-sensitive cases receiving CDK4/6 inhibitors is often shaped by later treatments, and a five-year observation window might prove inadequate given their generally better outlook. To date, no examination of these potential interactions has been conducted in Japanese cohorts, nor has any research addressed interactions between PPIs and abemaciclib. Accordingly, we proposed that parallel PPI therapy reduces the therapeutic value of CDK4/6 inhibitors. This investigation sought to determine, through analysis of routine clinical information, whether simultaneous PPI exposure modifies the clinical benefit of palbociclib or abemaciclib in hormone receptor-positive, HER2-negative metastatic breast cancer.

Materials and Methods

Study design

An observational, retrospective, multicenter case-control analysis was carried out at four facilities in Japan: National Cancer Center Hospital East (Chiba), Keio University Hospital (Tokyo), Miyagi Cancer Center (Miyagi), and Gifu University Hospital (Gifu). Clinical records from each site provided the source material. Centralized data compilation and statistical evaluation occurred at the Faculty of Pharmacy, Keio University (Tokyo). The reporting followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines [25].

Inclusion requirements comprised: (1) age 18 years or older with confirmed hormone receptor-positive, HER2-negative metastatic breast cancer (hormone receptor positivity required >1% expression of estrogen and/or progesterone receptors; HER2 negativity denoted immunohistochemistry scores of 0, 1+, or 2+ with negative in situ hybridization confirmation [11]); (2) initial exposure to palbociclib (125 mg oral daily for 21 days followed by 7 days rest in 28-day cycles) or abemaciclib (150 mg oral twice daily) combined with hormonal agents between December 2017 and August 2022; (3) administration during second-line or later hormonal treatment for de novo metastatic disease or progression on neoadjuvant therapy before surgery; (4) use in first-line or later settings for recurrence during or within 12 months after completing adjuvant hormonal therapy; and (5) second-line or later application for relapse occurring more than 12 months post-adjuvant completion. These classifications of treatment lines aligned with 2016 American Society of Clinical Oncology recommendations [26]. Adjustments to CDK4/6 inhibitor dosing and monitoring intervals were left to physician judgment based on individual response and tolerability.

Reasons for exclusion included: (1) patient objection to research use of records; (2) incomplete documentation; and (3) prior systemic chemotherapy for metastatic control (excluding neoadjuvant/adjuvant regimens).

Data collection

All patient information was anonymized. Variables gathered encompassed age, gender, menopausal state, Eastern Cooperative Oncology Group performance status, sites and count of metastases, relevant comorbidities (notably CDK4/6 inhibitor and PPI exposure), therapy sequence, dates of disease advancement or demise relative to CDK4/6 inhibitor

start, and grade 3 or higher toxicities during therapy or within 3 months afterward. Progression timing reflected the earliest evidence of advancement per Response Evaluation Criteria in Solid Tumors version 1.1 [27] on imaging or by clinical assessment. Toxicity grading utilized Common Terminology Criteria for Adverse Events version 5.0 [28]. Physicians routinely cautioned against potent cytochrome P450 3A4 modulators per available evidence. Cohorts were categorized as "PPI concomitant" when PPI coverage spanned the full duration or over 50% of CDK4/6 inhibitor exposure [15, 24], versus "no concomitant" for coverage below 50%. Visceral disease denoted involvement of lungs, liver, brain, pleura, or peritoneum. Observation concluded on November 30, 2022.

Endpoints

Primary effectiveness measures were progression-free and overall survival according to PPI exposure status. The tolerability measure involved adverse event profiles with versus without PPIs. Progression-free survival spanned from CDK4/6 inhibitor commencement to progression or death irrespective of cause. Overall survival extended from initiation to death from any etiology. Cases lacking progression or remaining alive were censored at final assessment for the respective outcomes.

Statistical analysis

Continuous baseline variables were summarized using medians accompanied by interquartile ranges, while categorical variables were expressed as percentages. Estimates of progression-free survival and overall survival were derived via the Kaplan-Meier approach, with group differences evaluated through log-rank testing. To address possible confounding arising from non-random assignment, propensity score matching was applied [29]. Logistic regression was employed to calculate propensity scores for PPI co-administration, incorporating selected variables deemed clinically relevant: patient age, Eastern Cooperative Oncology Group performance status (categorized as 0-1 versus 2), location of disease (visceral versus non-visceral), count of metastatic lesions, and prior endocrine therapy lines (1 versus ≥2). Additional robustness checks involved two distinct propensity score-based adjustments: (1) incorporation of the propensity score as a covariate within a multivariable Cox regression framework, and (2) application of inverse probability of treatment weighting (IPTW) [30]. Outcomes were reported as hazard ratios accompanied by 95% confidence intervals. In an exploratory posterior analysis, Bayesian probabilities for hazard ratios falling between 0.83 and 1.2 were calculated assuming a non-informative prior [31]. Duration of observation was determined via the reverse Kaplan-Meier technique [32]. Analyses were executed with SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA) and IBM SPSS Statistics version 29 (Armonk, NY, USA). All tests were two-tailed, with statistical significance defined at $P < 0.05$.

Ethics Statement

Central ethical clearance was granted by the Institutional Review Board of Keio University Faculty of Medicine (reference: 20221136). Subsequent approvals were secured from participating institutions. The investigation complied fully with the Declaration of Helsinki as well as Japan's Ethical Guidelines for Medical and Health Research Involving Human Subjects issued by the Ministries of Education, Culture, Sports, Science and Technology and Health, Labour and Welfare. Given the retrospective design, the ethics boards exempted the need for individual written consent. Instead, an opt-out opportunity was made available to potential participants via the websites of the respective hospitals.

Results and Discussion

Patient characteristics

The recruitment process is illustrated in **Figure 1**. From an initial screening of 596 individuals across the four centers, 240 satisfied inclusion requirements. Of these, 58 were receiving CDK4/6 inhibitors alongside PPIs. Following propensity score matching, the cohort was reduced to 112 cases, evenly allocated to PPI-exposed (n = 56) and PPI-unexposed (n = 56) arms. Post-matching propensity score distributions showed close overlap between arms (**Figure 1**). Demographic and clinical features at baseline are detailed in **Table 1.** Median patient age stood at 71 years (interquartile range, 61-75). Among 78 palbociclib recipients, 58 used the capsule formulation and 20 the tablet form. Roughly 70% of cases involved CDK4/6 inhibitors during first- or second-line hormonal treatment. Metastatic burden was limited to 5 or fewer sites, with visceral involvement present in over half the cohort. Dose reductions of CDK4/6 inhibitors were required in about two-thirds of patients in each arm, without notable intergroup differences in final

dosing. Fulvestrant comprised 66% of the partnered endocrine regimens. Lansoprazole accounted for 45% of PPI prescriptions.

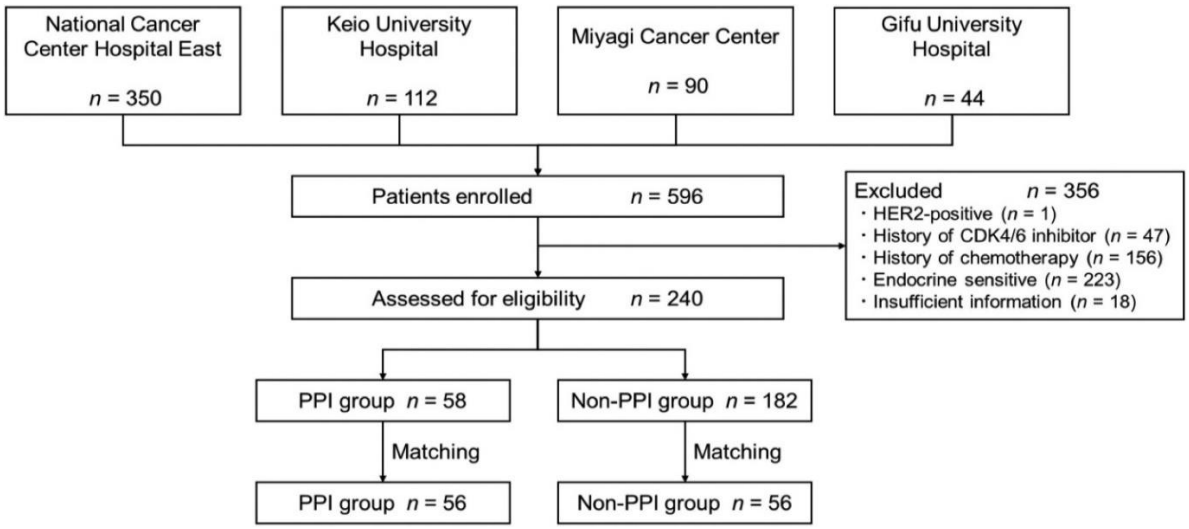


Figure 1. Patient enrollment flowchart. Abbreviations: HER2, human epidermal growth factor receptor type 2; CDK4/6, cyclin-dependent kinases 4 and 6; PPI, proton pump inhibitor.

Table 1. Patient characteristics.

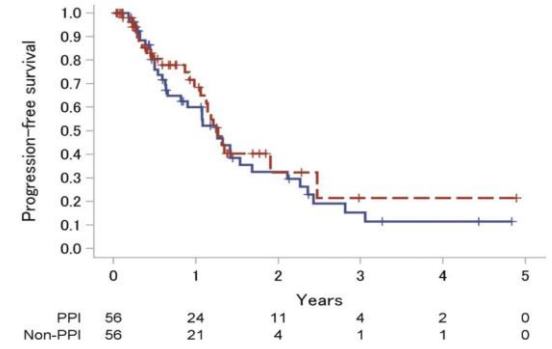
Baseline Demographics and Clinical Features	Balanced Cohort After Matching (n = 112)		Full Cohort Prior to Matching (n = 240)	
	PPI Users (n = 56)	Non-PPI Users (n = 56)	PPI Users (n = 58)	Non-PPI Users (n = 182)
Median age, years (interquartile range)[a]	71 (60-75)	70 (62-75)	71 (60-75)	62 (50-70)
Gender				
Women	55 (98)	55 (98)	57 (98)	180 (99)
Men	1 (2)	1 (2)	1 (2)	2 (1)
Menopausal status				
Premenopausal	8 (14)	4 (7)	8 (14)	47 (26)
Postmenopausal (or male)	48 (86)	52 (93)	50 (86)	135 (74)
ECOG performance status[a]				
0–1	52 (93)	53 (95)	52 (90)	178 (98)
2	4 (7)	3 (5)	6 (10)	4 (2)
Line of therapy[a]				
First-line	16 (29)	15 (27)	16 (28)	70 (39)
Second-line	23 (41)	26 (46)	25 (43)	70 (39)
Third-line or beyond	17 (30)	15 (27)	17 (29)	42 (23)
Median number of metastatic sites (interquartile range)[a]	2 (1-3)	2 (1-3)	2 (1-3)	2 (1-3)
Sites of metastasis[a]				
Visceral disease	34 (61)	36 (64)	36 (62)	107 (59)
Non-visceral disease only	22 (39)	20 (36)	22 (38)	75 (41)
CDK4/6 inhibitor used				
Palbociclib (capsule form)	33 (59)	25 (45)	34 (59)	91 (50)

Palbociclib (tablet form)	10 (18)	10 (18)	11 (19)	41 (23)
Abemaciclib	13 (23)	21 (38)	13 (22)	50 (28)
Dose reduction for CDK4/6 inhibitor				
Yes	36 (64)	40 (71)	36 (62)	125 (69)
No	20 (36)	16 (29)	22 (38)	57 (31)
Combined endocrine treatment				
Anastrozole	2 (4)	7 (13)	2 (3)	19 (10)
Letrozole	15 (27)	11 (20)	15 (26)	34 (19)
Exemestane	0	2 (4)	1 (2)	4 (2)
Tamoxifen	0	1 (2)	0	1 (1)
Fulvestrant	39 (70)	35 (63)	40 (69)	124 (68)
Use of LH–RH agonist				
None	49 (88)	53 (95)	51 (88)	139 (76)
Leuprorelin acetate	5 (9)	3 (5)	5 (9)	35 (19)
Goserelin acetate	2 (4)	0	2 (3)	8 (4)
Type of PPI prescribed				
Omeprazole	3 (5)		3 (5)	
Lansoprazole	25 (45)		27 (47)	
Rabeprazole	8 (14)		8 (14)	
Esomeprazole	10 (18)		10 (17)	
Vonoprazan	10 (18)		10 (17)	

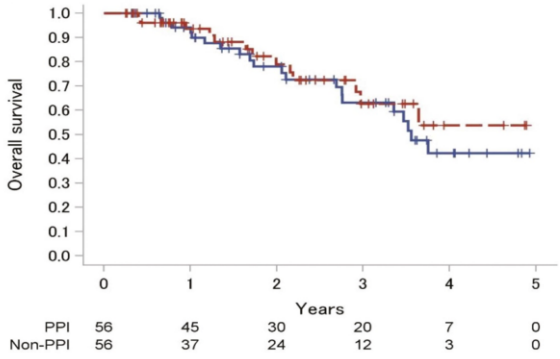
Abbreviations: IQR, interquartile range; PPI, proton pump inhibitor; ECOG PS, Eastern Cooperative Oncology Group performance status; CDK4/6 inhibitor, cyclin-dependent kinases 4 and 6; LH–RH, luteinizing hormone-releasing hormone. Data are presented as the number (%) of patients unless otherwise indicated. Percentages have been rounded and may not total 100. aAge, ECOG PS, treatment line, number of metastases, and metastatic sites were used to match the two groups.

Efficacy

Median observation duration reached 2.6 years (95% CI, 2.2-3.1). Progression-free survival medians were 1.2 years (95% CI, 0.7-1.7) in the PPI arm and 1.3 years (95% CI, 1.1-2.5) in the non-PPI arm (log-rank P = 0.53; **Figure 2).** Unadjusted hazard ratio was 1.19 (95% CI, 0.70-2.02). Overall survival median was 3.6 years (95% CI, 2.8-not reached) with PPIs versus not reached without (log-rank P = 0.57). Corresponding unadjusted hazard ratio stood at 1.23 (95% CI, 0.61-2.47).



a)



b)

Figure 2. Kaplan-Meier survival curves according to concomitant or non-concomitant PPI use. Kaplan-Meier survival curves were constructed according to the use of PPIs in the propensity score-matched

patients. Solid and dashed lines represent the PPI and non-PPI groups, respectively. The number of patients at risk are shown at the bottom. (a) Progression-free survival. (b) Overall survival. Abbreviation: PPI, proton pump inhibitor.

Robustness evaluations employing propensity score covariate adjustment and IPTW for progression-free survival yielded aligned findings (HR, 1.11; 95% CI, 0.73-1.68; P = 0.63 and HR, 1.09; 95% CI, 0.76-1.57; P = 0.62, respectively). Comparable consistency emerged for overall survival (HR, 1.21; 95% CI, 0.68-2.15; P = 0.51 and HR, 1.26; 95% CI, 0.71-2.24; P = 0.43, respectively). Bayesian posterior probabilities for progression-free survival hazard ratios within 0.83 to 1.2 varied between 42% and 77% **(Table 2).**

Table 2. HRs of PFS, OS, and the Bayesian posterior probability of HRs from 0.83 to 1.2.

	HR (95% CI)	Posterior probability (%)	*P*-value
PFS			
Propensity score matching	1.19 (0.70-2.02)	42	0.53
Multivariable analysis	1.11 (0.73-1.68)	57	0.63
IPTW	1.09 (0.76-1.57)	77	0.62
OS			
Propensity score matching	1.23 (0.61-2.47)	34	0.57
Multivariable analysis	1.21 (0.68-2.15)	39	0.51
IPTW	1.26 (0.71-2.24)	38	0.43

Abbreviations: HR, hazard ratio; CI, confidence interval; PFS, progression-free survival; OS, overall survival; IPTW, inverse probability of treatment weighting.

Separate subgroup evaluations were conducted for individuals receiving palbociclib (n = 177) and abemaciclib (n = 63) without applying propensity score matching. Among palbociclib-treated cases, median progression-free survival reached 1.3 years (95% CI, 0.6-2.3) with PPIs versus 1.1 years (95% CI, 0.9-1.3) without (**Figure 2**), showing no meaningful distinction (HR, 0.94; 95% CI, 0.61-1.46; P = 0.80). Overall survival likewise revealed no notable variance (HR, 1.47; 95% CI, 0.82-2.62; P = 0.19).

Comparable patterns emerged in the abemaciclib cohort (PFS: HR, 1.30; 95% CI, 0.53-3.17; P = 0.56; OS: HR, 1.22; 95% CI, 0.33-4.47; P = 0.76) **(Figure 3).**

Furthermore, 125 patients used the capsule formulation of palbociclib, while 52 received the tablet version. Assessments demonstrated no appreciable differences in progression-free or overall survival for capsules (PFS: HR, 1.06; 95% CI, 0.66-1.71; P = 0.80; OS: HR, 1.40; 95% CI, 0.76-2.58; P = 0.28) **(Figure 4).** Equivalent findings applied to tablets (data not presented).

Safety

Grade 3 or 4 toxicities in the matched cohort are outlined in **Table 3.** Occurrence rates remained comparable across each CDK4/6 agent irrespective of PPI exposure. Neutropenia predominated with palbociclib, whereas diarrhea was more frequent with abemaciclib. No substantial discrepancies existed between PPI and non-PPI arms (Fisher's exact test: P = 0.75 and P = 1.00, respectively). Fatal (grade 5) events were absent.

Table 3. Grade 3/4 adverse events.

Grade 3 or 4 Adverse Events	Abemaciclib Cohort (n = 34)		Palbociclib Cohort (n = 78)	
	PPI Users (n = 13)	Non-PPI Users (n = 21)	PPI Users (n = 43)	Non-PPI Users (n = 35)
Hematological adverse events				
Neutropenia	7 (54)	4 (19)	36 (84)	31 (89)
Leukopenia	2 (15)	0	20 (47)	11 (31)
Anemia	1 (8)	3 (14)	5 (11)	3 (9)
Thrombocytopenia	0	0	4 (9)	1 (3)
Febrile neutropenia	1 (8)	0	0	0
Non-hematological adverse events				

Diarrhea	3 (23)	4 (19)	1 (2)	0
Interstitial lung disease	0	2 (10)	3 (7)	2 (6)
Elevated AST	1 (8)	2 (10)	0	2 (6)
Elevated ALT	1 (8)	2 (10)	0	1 (3)
Stevens–Johnson syndrome	1 (8)	0	0	0
Skin ulceration	0	0	1 (2)	0
Fatigue	0	0	0	1 (3)
Skin infection	0	0	0	1 (3)
Appendicitis	0	0	0	1 (3)
Nausea	0	1 (5)	0	0
Loss of appetite	1 (8)	0	0	0

Abbreviations: PPI, proton pump inhibitor; AST, aspartate aminotransferase; ALT, alanine aminotransferase. Data are presented as the number (%) of patients.

Prior investigations have not specifically examined the link between parallel PPI administration and CDK4/6 inhibitor performance in chemotherapy-naïve, endocrine-resistant cases. Here, propensity score-matched comparisons indicated that PPI co-use failed to meaningfully impair progression-free or overall survival. Robustness checks and subgroup assessments reinforced these observations. This represents, to our knowledge, the initial multicenter real-world analysis in Japanese endocrine-resistant patients exploring survival impacts from PPIs combined with CDK4/6 inhibitors.

The cohort exhibited considerable uniformity, featuring numerous endpoint events for both progression-free and overall survival. Selection mirrored the chemotherapy-untreated, endocrine-resistant profile from the PALOMA-3 trial [5]. This design facilitated reliable assessment of whether PPI co-administration modifies palbociclib or abemaciclib outcomes; no significant efficacy gaps appeared across exposure status in supplementary evaluations. Findings contradicted our initial assumption of diminished CDK4/6 inhibitor benefit with PPIs. Pharmacokinetic data from Sun *et al*. [33] highlight formulation-specific effects: fasting co-administration of PPIs with palbociclib capsules reduced exposure by 62%, yet only 13% when taken post-meal. Proper fed-state intake may thus minimize clinical relevance of PPIs on palbociclib levels. Variability across interaction reports could stem from outpatient management differences internationally. Conducted in large Japanese university hospitals (>600 beds) and specialized oncology centers, care involved advanced oncology specialists. Notably, at National Cancer Center Hospital East, dedicated pharmacist counseling supported oral therapy adherence. Education critically influences compliance. Japanese hospital pharmacists deliver comprehensive medication instruction and monitoring [34]. A key systemic attribute is the dispensing-prescription separation, enabling community pharmacies to offer detailed outpatient guidance on oral antineoplastics [35]. Consequently, participants likely adhered well to post-meal capsule administration per labeling. Such elements probably contributed to preserved CDK4/6 inhibitor performance despite PPIs. Supporting this, dose adjustments occurred independently of PPI status—contrary to expectations if PPIs lowered drug exposure (which would spare more PPI users from reductions). Tolerability profiles also aligned between arms. Reduced exposure from PPIs should theoretically attenuate toxicity frequency and intensity, yet no such pattern materialized, aligning with the observed efficacy neutrality.

Currently, pharmacokinetic evidence regarding interactions between abemaciclib and PPIs remains unavailable. The tablet form of abemaciclib possesses weak basic properties, rendering its dissolution likely sensitive to pH variations. Structural parallels with palbociclib may account for the aligned outcomes observed. This represents, to our knowledge, the initial investigation documenting potential interactions involving abemaciclib and PPIs. Given abemaciclib's authorization for metastatic disease and adjuvant settings—allowing broader application than palbociclib [8, 9, 36]—these observations carry substantial practical relevance.

Earlier publications have indicated that parallel PPI administration compromises CDK4/6 inhibitor performance [14-16]. The current analysis aligns with those works in adopting a retrospective observational framework focused on hormone receptor-positive, HER2-negative metastatic cases. Nonetheless, discrepancies exist with other reports [21-24]. Diverging from our data, Lee *et al*. [16] identified interactions

between palbociclib capsules and PPIs across 1,310 individuals; employing propensity score matching, they determined that PPI co-use markedly diminished capsule efficacy, attributing this to impaired dissolution. However, reliance on claims databases precluded assessment of performance status or precise progression-free survival, leading to substitution with time to subsequent therapy—an imprecise surrogate. In contrast, our cohort incorporated both capsule (post-meal mandated) and tablet (meal-independent) palbociclib formulations without detecting efficacy impairment. Following the shift to tablets, interactions with PPIs appear clinically negligible for this agent.

Several strengths characterize this work. Primarily, recruitment spanned four Japanese facilities, enhancing representativeness for comparable real-world populations and supporting informed collaborative decisions among patients, physicians, pharmacists, and nursing staff—particularly for initiating frontline hormonal approaches in cases relapsing during or shortly after adjuvant therapy. Additionally, restriction to chemotherapy-naïve, endocrine-resistant individuals sharpened focus. The observation duration proved substantial, permitting evaluation of both progression-free and overall survival. Finally, propensity score matching achieved excellent balance between arms, bolstering result reliability and distinguishing this analysis.

Limitations

Certain constraints apply. The retrospective case-control observational design inherently invites recall and documentation biases. Sample size limited inclusion of further covariates in matching and prevented stratification by specific CDK4/6 agent. Adherence details for either CDK4/6 inhibitors or PPIs relied solely on dispensing records, precluding precise timing or compliance quantification. This constitutes an exploratory dataset requiring external confirmation. Direct drug exposure measurements were absent, necessitating dedicated prospective pharmacokinetic evaluations. Moreover, contemporary guidelines favor CDK4/6 inhibitors plus hormonal agents as initial therapy for hormone receptor-positive, HER2-negative disease, rendering investigations in endocrine-sensitive cohorts more pertinent to routine care than those restricted to resistant subgroups. Planned future efforts will address frontline outcomes in such populations.

Conclusion

Evidence from this analysis indicates that concurrent PPI exposure probably does not compromise CDK4/6 inhibitor outcomes in Japanese individuals with hormone receptor-positive, HER2-negative, endocrine-resistant metastatic breast cancer. Clinicians may reasonably maintain existing PPI regimens in patients prescribed palbociclib or abemaciclib without routine alteration. Results appear applicable within Japanese contexts and underscore the value of forthcoming prospective pharmacokinetic research.

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Ethics Statement: None

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