

# **A comparison between the adverse event profiles of patients receiving palbociclib and abemaciclib: analysis of the two real-world databases**

## **Abstract**

**Background:** Palbociclib and abemaciclib are cyclin-dependent kinase (CDK) 4/6 inhibitors currently used to treat breast cancer. Although their therapeutic efficacies are considered comparable, differences of adverse event (AE) profiles between the two drugs remain unclear.

**Aim:** We analysed two real-world databases, the World Health Organization's VigiBase and the Food and Drug Administration Adverse Event Reporting System (FAERS), to identify the differences in AE profiles between palbociclib and abemaciclib.

**Method:** Data of patients with breast cancer receiving palbociclib or abemaciclib recorded until December 2022 were extracted from the VigiBase and FAERS databases. In total, 200 types of AEs were analysed. The reporting odds ratios were calculated using a disproportionality analysis.

**Results:** Cytopenia was frequently reported in patients receiving palbociclib, while interstitial lung disease and diarrhoea were frequently reported in those receiving abemaciclib. Moreover, psychiatric and nervous system disorders were more common in the palbociclib group, whereas renal and urinary disorders were more common in the abemaciclib group.

**Conclusion:** This study was the first to show comprehensive disparities in the AE profiles between palbociclib and abemaciclib and highlighted the importance of considering these when selecting a suitable CDK4/6 inhibitor to ensure safe and favourable outcomes for patients with breast cancer.

## **Impact statements**

- In addition to cytopenia, many adverse events, including psychiatric and nervous system disorders, are potentially more frequent in patients receiving palbociclib compared to abemaciclib.

- 29 ● Interstitial lung disease, diarrhoea, and renal and urinary disorders are potentially more frequent in  
30 patients receiving abemaciclib compared to palbociclib.
- 31 ● The identification of adverse event profiles for palbociclib and abemaciclib contributes to drug  
32 selection that minimizes the risk of adverse events for individual patients.

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34

### 35 **Introduction**

36 Breast cancer is the most common cancer in females worldwide, with approximately 2.3 million  
37 cases annually [1]. Hormone receptor (HR) and human epidermal growth factor receptor 2 (HER2) are  
38 important biomarkers for classifying breast cancer subtypes, and approximately 70% of cases are classified  
39 as the HR-positive/HER2-negative subtype [2]. Currently, cyclin-dependent kinase 4/6 (CDK4/6) inhibitors,  
40 such as palbociclib (PAL) and abemaciclib (ABE), are used to treat HR-positive/HER2-negative breast  
41 cancers [2]. Various clinical trials have demonstrated that the combination of these CDK4/6 inhibitors with  
42 hormone therapy in HR-positive advanced breast cancer leads to extended progression-free survival and  
43 increased response rates compared with hormone therapy alone [3-8]. This highlights the efficacy of PAL  
44 and ABE in breast cancer treatment. However, to the best of our knowledge, clinical trials have yet to  
45 directly compare PAL and ABE or to establish distinguishable drug selection criteria. Since therapeutic  
46 efficacy is considered comparable between PAL and ABE, investigating the adverse event (AE) profiles  
47 may prove important during drug selection and treatment continuation. Typical AEs include  
48 myelosuppression with PAL [3] and diarrhoea and interstitial pneumonia with ABE [5, 6]; however,  
49 differences in real world AEs between PAL and ABE remain unclear.

50

### 51 **Aim**

52 This study compared the AE profiles associated with PAL and ABE using real-world data  
53 obtained from VigiBase, the World Health Organization's global Individual Case Safety Report database,  
54 and the Food and Drug Administration Adverse Event Reporting System (FAERS) database.

55

### 56 **Ethics approval**

57            Since this was an observational study that used completely anonymized patient data, the  
58 requirement for institutional review board approval was waived.

59

## 60 **Method**

61            Global drug safety data of PAL or ABE use recorded in VigiBase and FAERS before December  
62 2022 were analysed in this study. Data on age and sex were also collected. A flowchart of data extraction  
63 and data characteristics is presented in Supplementary Figure 1 and Supplementary Table 1, respectively.  
64 AEs and serious AEs listed in the drug information supplied by the manufacturers occurred in more than  
65 0.5% of patients receiving PAL or ABE were extracted. Each AE was considered a Preferred Term (PT) and  
66 categorized into System Organ Classes (SOCs) based on the Medical Dictionary for Regulatory Activities  
67 version 25.0. Duplicate PTs and PTs with < 10 cases in both the PAL and ABE groups were excluded to  
68 avoid false positives. In total, 200 types of PTs were analysed (Supplementary Table 2). The reporting odds  
69 ratios were calculated using a disproportionality analysis to compare the reported PT frequencies in both  
70 groups. *P* values < 0.01 were considered statistically significant and strictly enforced to reduce false  
71 positives. When calculating the reporting odds ratios and 99% confidence intervals, zero-cell corrections  
72 of 0.5 were added if any cell was equal to zero [9]. Statistical analyses were performed using EZR version  
73 1.61 (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [10].

74

## 75 **Results**

76            AE comparisons at the SOC level are presented in Figure 1. The superiority of the frequency of  
77 AEs at the SOC level was equivalent between the VigiBase and FAERS analyses. The disproportionality  
78 analysis revealed four SOC categories frequent in the ABE group (renal and urinary disorders, cardiac  
79 disorders, gastrointestinal disorders, and metabolic and nutritional disorders) and 12 categories that were  
80 frequent in the PAL group (nervous system disorders; blood and lymphatic system disorders; respiratory,  
81 thoracic, and mediastinal disorders; infections and infestations; general disorders and administration site  
82 conditions; vascular disorders; skin and subcutaneous tissue disorders; eye disorders; investigations;  
83 psychiatric disorders; musculoskeletal and connective tissue disorders; and injury, poisoning, and  
84 procedural complications).

85 AE comparison at the PT level using VigiBase and FAERS data are shown in Fig. 2 and  
86 Supplementary Fig. 2, respectively. All PT results are shown in Supplementary Table 3. Almost equivalent  
87 results were also obtained at the PT level in the analyses of VigiBase and FAERS. A reduction in white and  
88 red blood cell and platelet counts was frequent with PAL, while an increase in gamma-glutamyltransferase,  
89 alanine aminotransferase, and blood creatinine levels was frequent with ABE (Fig. 2a). Among the renal  
90 and urinary disorders, acute kidney injury and renal failure were common with ABE (Fig. 2b). PAL was  
91 frequently associated with gastrointestinal disorders, such as stomatitis and dyspepsia, while diarrhoea,  
92 abdominal pain, and vomiting were frequently associated with ABE (Fig. 2c). Among the respiratory,  
93 thoracic, and mediastinal disorders, many PTs, including dyspnoea and cough, were common with PAL,  
94 whereas interstitial lung disease and pneumonitis were common with ABE (Fig. 2d). Nervous system  
95 disorders, such as peripheral neuropathy and memory impairment, and psychiatric disorders, such as anxiety,  
96 depression, and insomnia, were frequent with PAL (Fig. 2e, f). Moreover, musculoskeletal, and connective  
97 tissue disorders (such as arthralgia and myalgia), infections and infestations (such as influenza and oral  
98 herpes), and general disorders and administration site conditions (such as fatigue and malaise) were  
99 common with PAL (Fig. 2g, h, i). Alopecia, hot flashes, and visual impairment were frequent with PAL,  
100 whereas dehydration and tachycardia were frequent with ABE (Fig. 2j).

101

## 102 **Discussion**

### 103 **Statement of Key Findings**

104 The study results indicated comprehensive disparities in the AE profiles between PAL and ABE.  
105 Many AEs, including cytopenia and nervous system and psychiatric disorders, were frequent with PAL,  
106 while interstitial lung disease, diarrhoea, and renal and urinary disorders were frequent with ABE.

107

### 108 **Strengths and Weaknesses**

109 This study had several limitations. First, although the VigiBase and FAERS databases are widely  
110 used in pharmacovigilance studies, the data are based on spontaneous reports, which can cause reporting  
111 bias, erroneous data, or missing data. Second, controlling confounding factors was more difficult in  
112 pharmacovigilance studies than in clinical trials, making it difficult to achieve the same level of rigor. Lastly,  
113 the data obtained from the databases did not include cases where AEs did not occur; thus, the incidence of

114 AEs could not be calculated. Hence, the results obtained in this study are qualitative rather than quantitative.  
115 Despite these limitations, this study can be sufficiently useful because it allows for a comprehensive  
116 analysis of multiple AEs using real-world data and for estimating the AE profile of PAL and ABE.

117

## 118 **Interpretation**

119 Although meta-analyses of clinical trials and retrospective studies conducted in the United States  
120 have compared the AE profiles of CDK4/6 inhibitors [11, 12], the current study analysed a large sample of  
121 global pharmacovigilance ABE or PAL data. To the best of our knowledge, this is the first study to  
122 comprehensively evaluate differences in AE frequency between PAL and ABE using a large-scale database,  
123 rather than relying on data from clinical trials or single-country study. The two databases used in this study,  
124 VigiBase and FAERS, were similar at the SOC level and mostly consistent at the PT level. Overall, this  
125 indicates increased reliability and certainty in our results.

126 According to a report summarizing previous clinical trials, neutropenia is more frequent in PAL,  
127 while diarrhoea, nausea, and liver dysfunction are more frequent in ABE [13]. The most common reasons  
128 for dose modification were myelosuppression for PAL and diarrhoea for ABE [14]. Therefore, these AEs  
129 affect tolerability. Severe interstitial pneumonia related to both PAL and ABE has been reported; however,  
130 its frequency has not been clear [13]. Our findings also revealed that cytopenia, alopecia, fatigue, and  
131 stomatitis were frequent in patients using PAL, whereas diarrhoea, vomiting, and liver dysfunction were  
132 frequent in patients using ABE. Additionally, the frequency of interstitial lung disease was higher for ABE.  
133 Overall, these results are consistent with those of previous reports and reflect clinical practice sufficiently.

134 Patients receiving ABE exhibited increased blood creatinine levels, renal failure, and acute  
135 kidney injury. Therefore, users of ABE may need to be treated with caution to prevent worsening of renal  
136 function. Although ABE-induced nephrotoxicity is considered rare, a case of grade 4 acute kidney injury  
137 has previously been reported [15]. ABE has been shown to inhibit creatinine transporters in renal tubules,  
138 resulting in decreased creatinine clearance and increased serum creatinine levels [16]. Other markers, such  
139 as blood urea nitrogen or cystatin C, may also be used to accurately assess renal function in patients  
140 undergoing ABE therapy.

141

## 142 **Further research**

143            Interestingly, in our study, patients receiving PAL frequently experienced psychiatric disorders.  
144    In particular, depression is associated with poor medication compliance and can affect cancer treatment  
145    outcomes [17]. Furthermore, other AEs likely to affect the quality of life of patients included peripheral  
146    neuropathy, dyspnoea, arthralgia, myalgia, and visual impairment with PAL and tachycardia with ABE.  
147    There are some limitations in the database analysis; therefore, further retrospective and prospective studies  
148    are needed to determine the disparity in AEs between both drugs.

149

### 150    **Conclusion**

151            This novel study used real-world data from Vigibase and FAERS to investigate the differences  
152    in AE profiles between patients treated with ABE and PAL. Although ABE and PAL have similar  
153    mechanisms of action and near-identical concomitant hormonal therapy efficacy, we highlighted the  
154    importance of carefully considering the differences in AEs between the two CDK4/6 inhibitors. By  
155    identifying the frequent AEs associated with each drug, clinicians can select medications that minimize the  
156    risk of problematic AEs, tailored to the patient's individual condition, which may lead to improved safety  
157    and more favourable drug therapy outcomes for patients with breast cancer.

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161

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164 **Competing Interests:** The authors have no conflicts of interest.

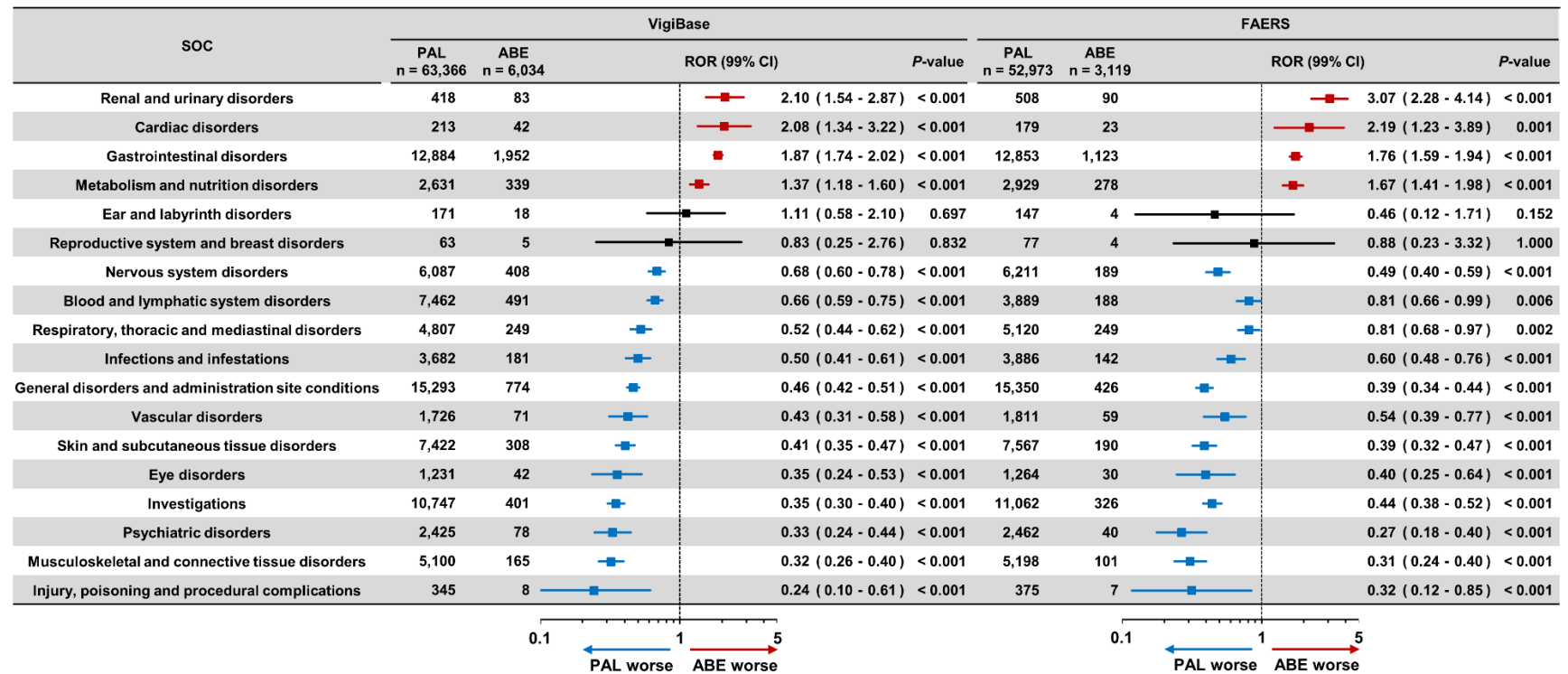
165 **References**

- 166 1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence  
167 and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021. DOI:  
168 10.3322/caac.21660.
- 169 2. Waks AG, Winer EP. Breast cancer treatment: a review. *JAMA* 2019. DOI: 10.1001/jama.2018.19323.
- 170 3. Finn RS, Martin M, Rugo HS, et al. Palbociclib and letrozole in advanced breast cancer. *N Engl J*  
171 *Med* 2016. DOI: 10.1056/nejmoa1607303.
- 172 4. Turner NC, Slamon DJ, Ro J, et al. Overall survival with palbociclib and fulvestrant in advanced  
173 breast cancer. *N Engl J Med* 2018. DOI: 10.1056/nejmoa1810527.
- 174 5. Sledge GW, Toi M, Neven P, et al. The effect of abemaciclib plus fulvestrant on overall survival in  
175 hormone receptor-positive, ERBB2-negative breast cancer that progressed on endocrine therapy-  
176 MONARCH 2: a randomized clinical trial. *JAMA Oncol* 2020. DOI: 10.1001/jamaoncol.2019.4782.
- 177 6. Goetz MP, Toi M, Campone M, et al. MONARCH 3: abemaciclib as initial therapy for advanced  
178 breast cancer. *J Clin Oncol* 2017. DOI: 10.1200/JCO.2017.75.6155.
- 179 7. Johnston SRD, Harbeck N, Hegg R, et al. Abemaciclib combined with endocrine therapy for the  
180 adjuvant treatment of HR+, HER2-, Node-Positive, High-Risk, Early Breast Cancer (monarchE). *J*  
181 *Clin Oncol* 2020. DOI: 10.1200/JCO.20.02514.
- 182 8. Johnston SRD, Toi M, O'Shaughnessy J, et al. Abemaciclib plus endocrine therapy for hormone  
183 receptor-positive, HER2-negative, node-positive, high-risk early breast cancer (monarchE): Results  
184 from a preplanned interim analysis of a randomised, open-label, phase 3 trial. *Lancet Oncol* 2023.  
185 DOI: 10.1016/S1470-2045(22)00694-5.
- 186 9. Weber F, Knapp G, Ickstadt K, et al. Zero-cell corrections in random-effects meta-analyses. *Res Synth*  
187 *Methods* 2020. DOI: 10.1002/jrsm.1460.
- 188 10. Kanda Y. Investigation of the freely available easy-to-use software 'EZ R' for medical statistics. *Bone*  
189 *Marrow Transplant* 2013. DOI: 10.1038/bmt.2012.244.
- 190 11. Onesti CE, Jerusalem G. CDK4/6 inhibitors in breast cancer: differences in toxicity profiles and  
191 impact on agent choice. a systematic review and meta-analysis. *Expert Rev Anticancer Ther* 2021.  
192 DOI: 10.1080/14737140.2021.1852934.

- 193 12. Price GL, Sudharshan L, Ryan P, et al. Real-world incidence and management of adverse events in  
194 patients with HR+, HER2- metastatic breast cancer receiving CDK4 and 6 inhibitors in a United  
195 States community setting. *Curr Med Res Opin* 2022. DOI: 10.1080/03007995.2022.2073122.
- 196 13. Tamura K. Differences of cyclin-dependent kinase 4/6 inhibitor, palbociclib and abemaciclib, in  
197 breast cancer. *Jpn J Clin Oncol* 2019. DOI: 10.1093/jjco/hyz151.
- 198 14. Braal CL, Jongbloed EM, Wilting SM, et al. Inhibiting CDK4/6 in breast cancer with palbociclib,  
199 ribociclib, and abemaciclib: similarities and differences. *Drugs* 2021. DOI: 10.1007/s40265-020-  
200 01461-2.
- 201 15. Da Silva A, Chretien B, Alexandre J, et al. Abemaciclib-induced reversible grade 4 nephrotoxicity.  
202 *Breast J* 2020. DOI: 10.1111/tbj.13980.
- 203 16. Chappell JC, Turner PK, Pak YA, et al. Abemaciclib inhibits renal tubular secretion without changing  
204 glomerular filtration rate. *Clin Pharmacol Ther* 2019. DOI: 10.1002/cpt.1296.
- 205 17. Grenard JL, Munjas BA, Adams JL, et al. Depression and medication adherence in the treatment of  
206 chronic diseases in the United States: a meta-analysis. *J Gen Intern Med* 2011. DOI: 10.1007/s11606-  
207 011-1704-y.

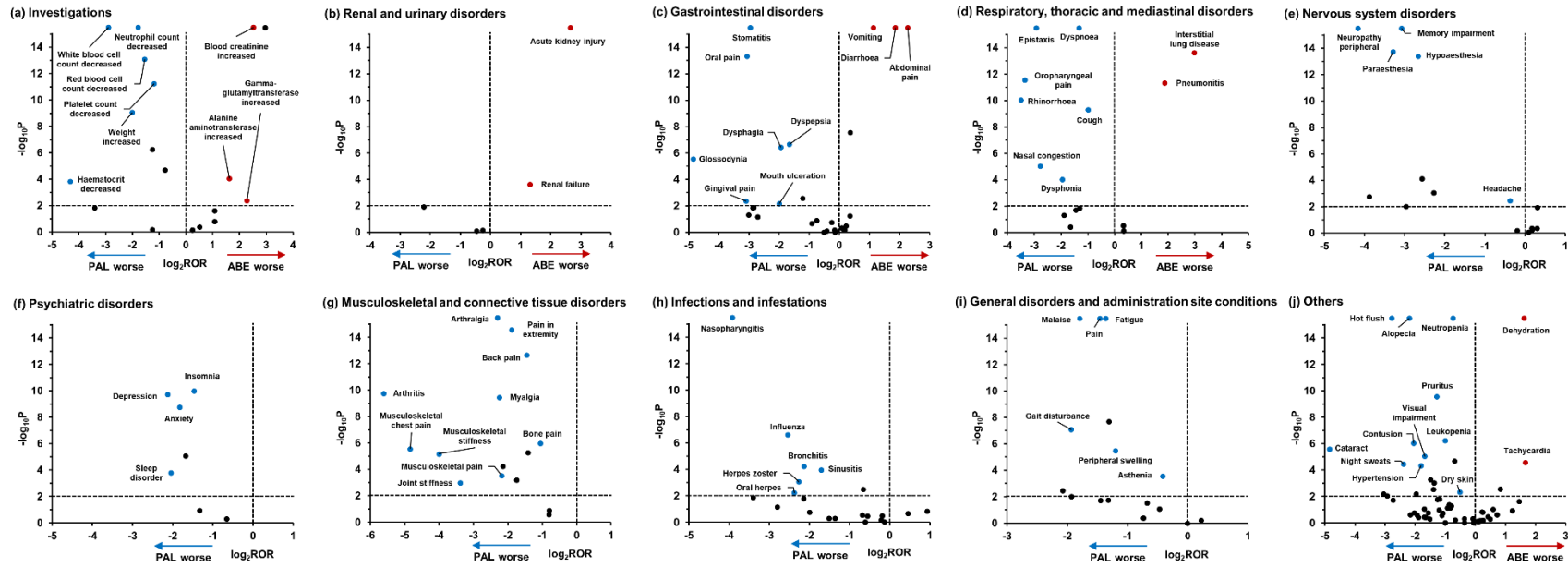
208 **Figures**

209 **Fig. 1**



210  
 211 Comparison of adverse events between palbociclib (PAL) and abemaciclib (ABE) classified by the System Organ Class (SOC). The plots show the reporting odds  
 212 ratio (ROR) with 99% confidence interval (CI) on a logarithmic scale

213 **Fig. 2**



214  
 215 Comparison of adverse events between palbociclib (PAL) and abemaciclib (ABE) at the Preferred Term level using VigiBase. Data are shown according to the  
 216 following System Organ Classes: (a) investigations, (b) renal and urinary disorders, (c) gastrointestinal disorders, (d) respiratory, thoracic, and mediastinal disorders,  
 217 (e) nervous system disorders, (f) psychiatric disorders, (g) musculoskeletal and connective tissue disorders, (h) infections and infestations, (i) general disorders and  
 218 administration site conditions, and (j) others. Preferred Terms with  $P < 0.01$  in both VigiBase and Food and Drug Administration Adverse Event Reporting System  
 219 are labelled