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Adverse event profiles of CDK4/6 inhibitors: data mining and disproportionality analysis of the FDA adverse event reporting system

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Abstract

Background: Cyclin-dependent kinases 4 and 6 (CDK4/6) inhibitors are targeted therapies designed to selectively block CDK4/6, crucial regulators of the cell cycle. These inhibitors play a pivotal role in restoring cell cycle control, particularly in breast cancer cases marked by abnormal CDK regulation, ultimately inhibiting uncontrolled cell division and tumor growth.

Objectives: This analysis aimed to comprehensively examine adverse effects in CDK4/6 inhibitors using the United States Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) database.

Design: Disproportionality analysis was conducted to analyze the adverse event (AE) reports related to CDK4/6 inhibitor submitted to the FAERS database.

Methods: We collected AE reports regarding palbociclib, ribociclib, abemaciclib, trilaciclib, and dalpiciclib submitted to the FAERS from 2015Q1 to 2023Q1. We used the system organ class and the Standardized MedDRA Query to perform a comprehensive search for AEs at the preferred term (PT) level, using case reports as our data source. After removing duplicate reports, we performed disproportionality analysis and sensitivity analysis to identify safety signals.

Results: A total of 85,635 reports encompassing 280,211 AEs were extracted for analysis. Among 3681 scrutinized PTs, approximately 484 were detected as statistically significant signals associated with CDK4/6 inhibitors. It was noteworthy that palbociclib and ribociclib had comparable safety profiles, whereas abemaciclib exhibited distinctive safety patterns. Notably, our analysis found novel safety signals linked to CDK4/6 inhibitors, including nail-related disorders such as onychoclasis, nail disorder, and nail discoloration, and psychiatric concerns, including eating disorders and emotional disorder.

Conclusion: Overall, the present study identified several new safety signals of CDK4/6 inhibitors, as well as differences among various drugs within the CDK4/6 category, through the use of the FDA FAERS, which deserve more careful monitoring in the clinic.

Plain language summary

A study on the adverse effects of CDK4/6 inhibitors

Introduction: An adverse event (AE) refers to any undesirable or harmful occurrence that happens to an individual during or after the use of a medical product or intervention. These events are typically reported to regulatory authorities, such as the Food and Drug Administration (FDA), to ensure the safety and effectiveness of medical products. The United States Food and Drug Administration Adverse Event Reporting System (FAERS) database plays a pivotal role in identifying these adverse events. Cyclin-dependent kinases 4 and 6 (CDK4/6) inhibitors are a class of drugs used to treat certain types of cancer by inhibiting the growth and division of cancer cells. This study investigated the safety signals related to CDK4/6 inhibitors, including palbociclib, ribociclib, abemaciclib, and trilaciclib, by using the FAERS database.

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Methods: We collected AE reports associated with CDK4/6 inhibitors that were submitted to the FAERS database between the first quarter of 2015 and the first quarter of 2023. Reporting odds ratio (ROR) method was used identify signals of AEs.
Results: 85,635 AE reports were identified, approximately 484 AE terms were identified as positive signals. Palbociclib and ribociclib had similar safety profiles, while abemaciclib showed a unique pattern. Our analysis also revealed previously unreported AEs, including nail-related disorders such as onychoclasis, nail disorder and nail discolouration. Psychiatric concerns such as eating disorders and emotional disorder were also identified.
Conclusion: We discovered important safety concerns related to CDK4/6 inhibitors. Some of these concerns were consistent with previous studies, while nail-related disorders, eating disorder and emotional disorder were new and not mentioned in the drug labels or existing literature. Our findings may help physicians and pharmacists to weigh the risks and benefits of using CDK4/6 inhibitors in clinical practice.

Keywords: CDK4/6 inhibitor, drug safety, FAERS, pharmacovigilance, signal

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Introduction

Cyclin-dependent kinases 4 and 6 (CDK4/6) inhibitors are a type of targeted medicines for breast cancer that selectively inhibit CDK4/6, which are the key regulators of the cell cycle. The primary function of CDK4 and CDK6 is to help control the progression of cells from the G1 phase (the initial phase of cell division) into the S phase (the phase where DNA replication occurs). In cancer, abnormal regulation of these CDKs may lead to uncontrolled cell division and tumor growth. By blocking CDK4/6, these inhibitors can restore the cell cycle and effectively block cell proliferation in a variety of tumor cells, including those of breast cancer cells. CDK4/6 inhibitors have shown good efficacy in patients with HR+/HER2− breast cancer in a number of clinical trials.[1]

Five CDK4/6 inhibitors are currently marketed worldwide, four of which are used for the treatment of HR+/HER2− breast cancer: palbociclib (Ibrance®; Pfizer, Inc., New York, United States), ribociclib (Kisqali®; Novartis International AG, Basel, Switzerland), abemaciclib (Verzenio®; Eli Lilly and Company, Basingstoke, United Kingdom), and dalpiciclib (Erlikon®; Jiangsu Hengrui Medicine Co Ltd., Lianyungang, China).[2,3] Furthermore, trilaciclib (Cosela®; G1 Therapeutics, Inc. and Simcere Pharmaceutical Group Ltd. Triangle Park, United States) exhibits substantial different from other inhibitors utilized for small-cell lung cancer and chemotherapy induced myelosuppression).[4] Among CDK4/6 inhibitors, abemaciclib displayed the most potent activity toward CDK4 and CDK6 and a lower incidence of severe myelosuppression and neutropenia.[5–7]

We reviewed several clinical trials and found that the most common adverse events (AEs) of palbociclib[8–11] were neutropenia, infections, leukopenia, fatigue, nausea, stomatitis, anemia, alopecia, diarrhea, thrombocytopenia, rash, vomiting, decreased appetite, asthenia, and pyrexia. The most common AEs of ribociclib,[12–14] including laboratory abnormalities, were decreased leukocytes, decreased neutrophils, decreased hemoglobin, decreased lymphocytes, increased alanine aminotransferase, increased aspartate aminotransferase, infections, nausea, fatigue, decreased platelets, diarrhea, headache, alopecia, vomiting, back pain, constipation, cough, rash, creatinine increased, and abdominal pain. Abemaciclib has been studied in a variety of tumors to date, including breast cancer, melanoma, bladder cancer, p16 ink4A-deficient mesothelioma, non-small cell lung cancer, and oral squamous cell carcinoma.[15–17] The most common AEs in various studies were fatigue, gastrointestinal reactions (diarrhea, nausea, vomiting, anorexia, etc.), and hematologic adverse reactions (leukopenia, neutropenia, thrombocytopenia, anemia, etc.).[16] The route of administration and the indications of trilaciclib differ from others, and its AEs were significantly different from the

three drugs mentioned above. The most common AEs (⩾10% of patients with ⩾2% difference in incidence vs placebo) were fatigue, hypocalcemia, hypokalemia, hypophosphatemia, increased aspartate aminotransferase, headache, and pneumonia.[18–21]

Adverse drug reaction (ADR) signal finding is an important research method to evaluate the post-marketing safety of drugs and can reflect the real situation of drugs in practical use. Mining the data of spontaneous reporting system with relevant technology helps to identify the potential ADRs earlier and reevaluate the known ADRs as well. The Food and Drug Administration Adverse Event Reporting System (FAERS) is one of the key databases used for identifying potential association between drugs and AEs in post-marketing surveillance of drug safety.[22] Some published FAERS analyses of CDK4/6 inhibitors have focused on AEs of special interest or specific events.[23–25] Data on the real-world safety profile of CDK4/6 inhibitors were still lacking.

Therefore, the aim of this paper is to analyze and evaluate the alert signals of CDK4/6 inhibitors in FAERS using data mining technology and further explore the safety issues in clinical use.

Materials and methods

Data source

We downloaded the FAERS data files from https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html. The pharmaceutical agents under studied in our research were palbociclib, ribociclib, abemaciclib, trilaciclib, and dalpiciclib, which were launched in February 2015, March 2017, September 2017, March 2021, and December 2021, respectively. Therefore, the data we have selected spanned from the first quarter of 2015 to the first quarter of 2023.

Within the FAERS database, the reported drug names are variable and include fields for generic names (such as palbociclib, abemaciclib, ribociclib, trilaciclib, and dalpiciclib) in the "pro_ai" field, as well as generic names, brand names, and other possible denominations (Ibrance, Itulsi, Verzenio, Verzenios, Yulareb, Kisqali, Kryxana, Cosela, Bdpalbo, Paleno, Primcyv, and Erlikon) in the "drug-name" field. Our analysis only includes reports where CDK4/6 inhibitors are the primary suspect (PS) drugs.

The FAERS database utilizes the MedDRA terminology developed by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) to facilitate the coding and statistical analysis of AEs and the structured processing of raw data. MedDRA, a product of ICH's efforts to establish a standardized global medical terminology, serves as a pivotal tool for regulatory communication and the evaluation of data pertaining to medicinal products for human use.[26] Beyond its standardized coding and processing functions, MedDRA offers valuable classification information for AEs. Therefore, we used MedDRA version 26.0 (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, Geneva, Switzerland) to autonomously categorize AEs into the broadest classifications, namely, system organ class (SOC) and preferred term (PT). These SOC and PT classifications are widely recognized and employed in the analysis of data from the Food and Drug Administration (FDA) FAERS. To avoid duplicating PTs in SOC, when a PT belongs to multiple SOC categories, it is classified under the primary SOC. Furthermore, we conducted query analyses employing Standardized MedDRA Queries (SMQs) to investigate specific categories of interest.

Data cleaning

In the context of this study, the analyzed reports include three key elements: identifiable patients, suspected medications, and AE reports. Following the guidelines established by the FDA for the elimination of duplicate reports, the most recent Case ID was used for disproportionate analysis. AEs associated with off-label use, product issues, medication errors, and those related to breast cancer were excluded from the analysis. Consequently, our analysis focused exclusively on drug-induced AEs, excluding those associated with the patients' underlying medical conditions. Specifically excluded SOCs were: (a) congenital, familial, and genetic disorders; (b) injury, poisoning, and procedural complications; (c) neoplasms benign, malignant and unspecified (incl cysts and polyps); (d) pregnancy, puerperium, and perinatal conditions; (e) product issues; (f) reproductive system and breast disorders; (g) social circumstances; and (h) surgical and medical procedures.

Table 1. Fourfold table for ROR calculation.

Type of drug	Target adverse reaction reports	Other adverse reaction reports	Sum
Target drug	a	b	$a+b$
Other drug	c	d	$c+d$
Sum	$a+c$	$b+d$	$n=a+b+c+d$

ROR, reporting odds ratio.

Data mining

Disproportionality analysis, including algorithms of reporting odds ratio (ROR), proportional reporting ratio (PRR), and Bayesian confidence propagation neural network (BCPNN), is an important tool to identify safety signals. Because of the advantages of calculating ROR in spontaneous report databases,[27] the ROR values were used as the main signal detection metric in our study. ROR calculation is mainly based on a fourfold table as Table 1.

The ROR value is calculated as:

$$\mathrm{ROR} = \frac{(a/c)}{b/d} = \frac{ad}{bc}$$

$$95\%\,\mathrm{CI} = e^{\ln(\mathrm{ROR}) \pm 1.96\sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}}.$$

ROR values were calculated for each PT. In addition, we also calculated PRR values and information component (IC) values of BCPNN method and compared the signals result with the signals found by ROR values. Supplemental Table S1 displayed the criteria and equations employed in the aforementioned algorithms.

Data import and extraction were conducted through MySQL version 15.0 (Oracle Corporation, Redwood City, United States) and Navicat Premium 15 (PremiumSoft CyberTech Ltd., Hong Kong, China), while statistical analyses were carried out employing Microsoft Excel 2021 (Microsoft Corporation, Washington, United States).

Sensitivity analysis

A sensitivity analysis[28] was conducted to evaluate the influence of concomitant medications on the study new signals outcomes. The identification of concomitant drugs was based on the examination of raw data retrieved from Drug tables. Subsequently, the occurrence of specific events was verified by the drug labels. Drugs found to be listed in the labels were subsequently excluded from the analysis.

Results

Basic characteristics of reported CDK4/6 inhibitor related AE

From the beginning of January 1, 2015 through the end of March 31, 2023, a total of 85,635 reports with 280,211 AEs were obtained for analysis. Predominantly, the afflicted individuals were of the female gender, comprising a majority percentage of 92.91%, while a minority faction of 4.86% exhibited an undisclosed gender identity. It is noteworthy that individuals aged over 50 years of age accounted for a substantial proportion of the AE reports, contributing a notable 68.73% of the total.

Among the AEs cataloged, hospitalization was the most frequently documented serious outcome, accounting for 15.22% of the reports. Death from AEs occurred in 13.30% of the reported cases. The sources of these reports were primarily healthcare professionals, including physicians, nurses, pharmacists, and other healthcare professionals, accounting for 52.44% of the submissions, and consumers, who accounted for 43.99% of the reports. Notably, a substantial proportion of the reports originated from the United States, with a remarkable 72.04% share of the comprehensive dataset. Table 2 presents a detailed analysis of patient demographics and AE reports related to the use of CDK4/6 inhibitors.

The case counts for each drug are as follows: palbociclib (212,350), ribociclib (50,864), abemaciclib (16,663), and trilaciclib (334). It is

Table 2. Characteristics of reports associated with CDK4/6 inhibitors from 2015Q1 to 2023Q1.

Characteristic	CDK4/6 inhibitors	Palbociclib	Ribociclib	Abemaciclib	Trilaciclib
Number of reports	85,635	66,466	11,476	7578	115
Gender, *n* (%)					
Female	79,561 (92.91)	62,182 (93.55)	10,576 (92.16)	6779 (89.46)	24 (20.87)
Male	1911 (2.23)	1524 (2.29)	231 (2.01)	129 (1.70)	27 (23.48)
Unknown	4163 (4.86)	2760 (4.15)	669 (5.83)	670 (8.84)	64 (55.65)
Age, *n* (%)					
<20	94 (0.11)	72 (0.11)	19 (0.17)	3 (0.04)	0 (0.00)
20–29	187 (0.22)	141 (0.21)	37 (0.32)	8 (0.11)	1 (0.87)
30–39	1838 (2.15)	1372 (2.06)	352 (3.07)	112 (1.48)	2 (1.74)
40–49	5739 (6.70)	4521 (6.80)	848 (7.39)	362 (4.78)	8 (6.96)
50–59	13,252 (15.47)	11,238 (16.91)	1223 (10.66)	786 (10.37)	5 (4.35)
60–69	20,601 (24.06)	18,014 (27.10)	1481 (12.91)	1094 (14.44)	12 (10.43)
70–79	17,440 (20.37)	15,392 (23.16)	1175 (10.24)	867 (11.44)	6 (5.22)
⩾80	7558 (8.83)	6842 (10.29)	369 (3.22)	345 (4.55)	2 (1.74)
Unknown	18,926 (22.10)	8874 (13.35)	5972 (52.04)	4001 (52.80)	79 (68.70)
Outcome, *n* (%)					
Hospitalization	13,030 (15.22)	8737 (13.15)	2629 (22.91)	1614 (21.30)	50 (43.48)
Death	11,390 (13.30)	8260 (12.43)	2452 (21.37)	665 (8.78)	13 (11.30)
Reported countries, *n* (%)					
USA	61,688 (72.04)	52,019 (78.26)	4259 (37.11)	5318 (70.18)	92 (80)
Reported person, *n* (%)					
Consumer	37,670 (43.99)	28,461 (42.82)	5819 (50.71)	3360 (44.34)	30 (26.09)
Physician	13,044 (15.23)	8906 (13.40)	2997 (26.12)	1097 (14.18)	44 (38.26)
Health professional	13,139 (15.34)	10,705 (16.11)	1276 (11.12)	1130 (14.91)	28 (24.35)
Pharmacist	9674 (11.30)	8527 (12.83)	414 (3.61)	721 (9.51)	12 (10.43)
Other health professional	9202 (10.75)	7945 (11.95)	747 (6.51)	510 (6.73)	0 (0.00)
Unknown	2903 (3.39)	1919 (2.89)	223 (1.94)	760 (10.03)	1 (0.87)

CDK4/6, cyclin-dependent kinases 4 and 6.

noteworthy that relevant pharmacovigilance data were lacking for dalpiciclib due to its relatively recent introduction to the market.

Additionally, our results indicated that trilaciclib differed significantly from palbociclib and abemaciclib in terms of AE. Trilaciclib has a notable number of events, including dyspnea, decreased platelet count, myelosuppression, pneumonia, anemia, and chest discomfort, which were higher in incidence. However, due to the limited total number of AEs, these data may not be conclusive.

AEs classified by SOC and PT

Figure 1 illustrates the AE distribution associated with CDK4/6 inhibitors, namely palbociclib, abemaciclib, ribociclib, and trilaciclib, categorized by SOCs. The CDK4/6 inhibitor-related AEs were found to be predominantly associated with SOCs such as general disorders and administration site conditions (20.40%) and gastrointestinal disorders (15.20%) as well.

In the evaluation of 3681 potential targets (PTs) related to CDK4/6 inhibitors, the numbers of positive signals detected by the different methods were as follows: ROR: 484, PRR: 309, and BCPNN: 445 (see Supplemental Table S2). The positive signals detected by ROR are highly consistent with the positive signals identified by BCPNN, and they all include the positive signals identified by PRR. Kenneth's research underscores the superiority of ROR in spontaneous report databases over PRR.[26] Consequently, we have chosen to use ROR-derived results in our analysis. Table 3 provides a comprehensive analysis of the top 50 most frequently reported PTs, offering insights based on the frequency of occurrence in the dataset.

General disorders and administration site conditions. The most common AEs documented in association with CDK4/6 inhibitors included fatigue (13,194 events), decreased white blood cell count (9846 events), nausea (7963 events), diarrhea (6854 events), and alopecia (5523 events). It is noteworthy that about seven of the most frequently encountered PTs within the top 50 were associated with general disorders, as shown in Table 3.

The AEs associated with palbociclib that have the highest occurrence were fatigue, decreased white blood cell count, nausea, alopecia, and diarrhea, and they belong to diverse SOCs. Top five PTs of ribociclib were nausea, fatigue, neutropenia, vomiting, and decreased white blood cell count. The top five AEs associated with abemaciclib were diarrhea, nausea, fatigue, vomiting, and decreased appetite; except for fatigue, all of them are related to gastrointestinal adverse reactions.

In the context of the SOC classification under "general disorders and administration site conditions," CDK4/6 inhibitors exhibited AEs as follows: fatigue ($n = 13{,}194$, ROR = 3.74), asthenia ($n = 3230$, ROR = 1.97), malaise ($n = 3241$, ROR = 1.50), pyrexia ($n = 1617$, ROR = 1.09), feeling abnormal ($n = 1343$, ROR = 1.15), and peripheral swelling ($n = 1120$, ROR = 1.14), while other AEs, pain ($n = 3141$, ROR = 1.02), fall within a 95% confidence interval of less than 1. In this SOC category, abemaciclib appears to have significant differences compared to other drugs. Within this category, the only meaningful PTs were fatigue and asthenia, with the ROR for other PTs being less than 1. The distribution of the top 10 reported AEs related to general disorders and administration site conditions, along with their respective proportional representation, is shown in Figure 2.

Gastrointestinal disorders. Gastrointestinal disorders emerged as the predominant SOC frequently associated with CDK4/6 inhibitors. Within this SOC, a majority of PTs were linked to gastrointestinal nonspecific inflammation and dysfunctional conditions, as shown in Table 3. We performed an analysis based on the SMQs to summarize all instances of gastrointestinal nonspecific inflammation and dysfunction. The distribution of the top 10 reported AEs related to gastrointestinal non-specific inflammation and dysfunction, along with their respective proportional representation, is shown in Figure 3. These events included nausea, diarrhea, vomiting, constipation, abdominal discomfort, and others. Notably, among these PTs, diarrhea showed a pronounced frequency and robust signal association with abemaciclib ($n = 2028$, ROR = 12.71), while stomatitis displayed a strong signal correlation with palbociclib ($n = 2147$, ROR = 10.53). For comprehensive information, including the detailed report counts and relative RORs for all gastrointestinal non-specific inflammation and dysfunction AEs, see Supplemental Table S3.

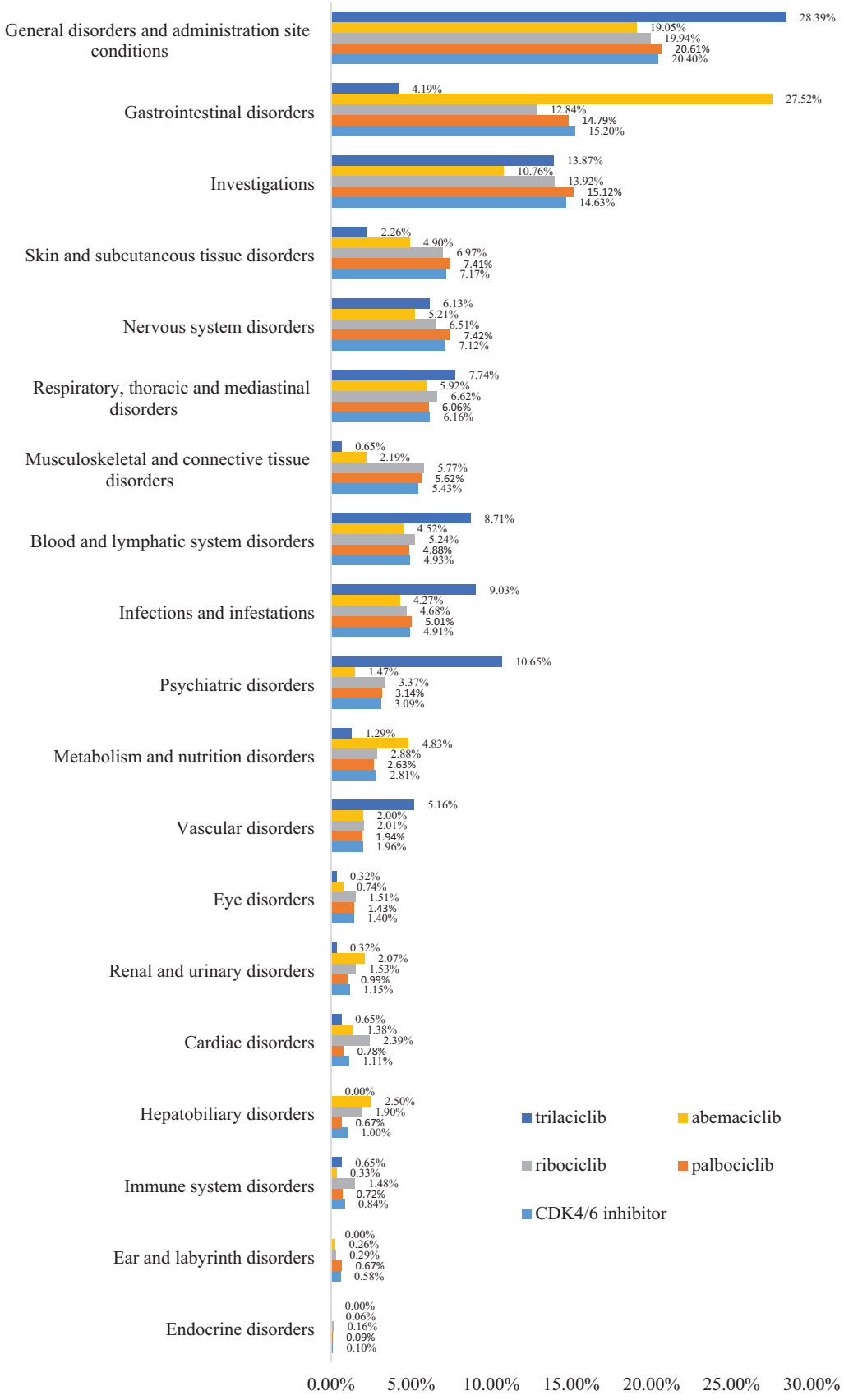

Figure 1. Proportion of adverse events classified by system organ class.

Table 3. Signal strength for CDK4/6 inhibitors at the top 50 high-frequency PT level in FAERS.

SOC	PT	CDK4/6 inhibitor		Palbociclib		Ribociclib		Abemaciclib		Trilaciclib	
		N	ROR (95% CI)	*N*	ROR (95% CI)	*N*	ROR (95% CI)	*N*	ROR (95% CI)	*N*	ROR (95% CI)
General disorders and administration site conditions	Fatigue	13,194	3.74 (3.67, 3.80)	11,438	4.30 (4.22, 4.38)	1240	1.85 (1.75, 1.96)	509	2.33 (2.14, 2.55)	7	1.58 (0.75, 3.35)
	Malaise	3241	1.50 (1.45, 1.56)	2553	1.56 (1.50, 1.62)	569	1.45 (1.33, 1.57)	113	0.87 (0.73, 1.05)	6	2.34(1.04, 5.24)
	Asthenia	3230	1.97 (1.90, 2.04)	2514	2.02 (1.94, 2.10)	511	1.70 (1.56, 1.86)	200	2.04 (1.77, 2.34)	5	2.55 (1.05, 6.16)
	Pain	3141	1.02 (0.99, 1.06)	2421	1.04 (1.00, 1.08)	629	1.13 (1.04, 1.22)	84	0.46 (0.37, 0.57)	7	1.93 (0.91, 4.08)
	Pyrexia	1617	1.09 (1.04, 1.14)	1175	1.04 (0.98, 1.11)	370	1.37 (1.24, 1.52)	71	0.80 (0.64, 1.01)	1	/
	Feeling abnormal	1343	1.15 (1.09, 1.22)	996	1.13 (1.06, 1.20)	287	1.36 (1.21, 1.53)	60	0.86 (0.67, 1.11)	0	—
	Peripheral swelling	1120	1.21 (1.14, 1.29)	822	1.17 (1.10, 1.26)	247	1.47 (1.30, 1.67)	51	0.93 (0.70, 1.22)	0	—
Gastrointestinal disorders	Nausea	7963	2.33 (2.27, 2.38)	6119	2.35 (2.29, 2.41)	1268	2.01 (1.90, 2.13)	569	2.78 (2.56, 3.03)	7	1.68 (0.80, 3.56)
	Diarrhea	6854	2.31 (2.26, 2.37)	4148	1.83 (1.77, 1.88)	677	1.23 (1.14, 1.33)	2028	12.71 (12.13, 13.31)	1	—
	Vomiting	3429	1.76 (1.70, 1.82)	2250	1.51 (1.45, 1.58)	772	2.17 (2.03, 2.33)	403	3.50 (3.17, 3.86)	4	1.71 (0.64, 4.58)
	Constipation	2506	2.64 (2.54, 2.75)	2011	2.80 (2.67, 2.92)	376	2.16 (1.95, 2.39)	119	2.08 (1.74, 2.49)	0	—
	Stomatitis	2292	8.53 (8.17, 8.90)	2147	10.53 (10.08, 11.01)	95	1.82 (1.49, 2.23)	50	2.93 (2.22, 3.87)	0	—
	Abdominal discomfort	1314	1.58 (1.49, 1.66)	1002	1.58 (1.49, 1.69)	236	1.55 (1.37, 1.77)	76	1.53(1.22, 1.91)	0	—
	Abdominal pain upper	1115	1.23 (1.15, 1.30)	764	1.11 (1.03, 1.19)	204	1.23 (1.07, 1.41)	147	2.73 (2.32, 3.21)	0	—
Investigations	White blood cell count decreased	9846	23.79 (23.27, 24.31)	8899	28.10 (27.46, 28.75)	714	7.93 (7.36, 8.54)	226	7.60 (6.67, 8.67)	7	11.80 (5.58, 24.95)
	Full blood count abnormal	2148	15.54 (14.85, 16.26)	2052	19.55 (18.67, 20.48)	56	1.98 (1.52, 2.57)	40	4.32 (3.17, 5.90)	0	—
	Platelet count decreased	2003	4.34 (4.15, 4.54)	1649	4.69 (4.47, 4.93)	237	2.75 (2.42, 3.13)	107	3.79 (3.14, 4.59)	10	18.09 (9.64, 33.95)
	Neutrophil count decreased	1921	12.00 (11.45, 12.58)	1594	12.95 (12.30, 13.63)	260	8.27 (7.32, 9.35)	62	5.96 (4.64, 7.65)	5	24.20 (10.01, 58.54)

(Continued)

Table 3. (Continued)

SOC	PT	CDK4/6 inhibitor		Palbociclib		Ribociclib		Abemaciclib		Trilaciclib	
		N	ROR (95% CI)	*N*	ROR (95% CI)	*N*	ROR (95% CI)	*N*	ROR (95% CI)	*N*	ROR (95% CI)
	Weight decreased	1780	1.40 (1.33, 1.46)	1349	1.39 (1.32, 1.47)	267	1.15 (1.02, 1.30)	159	2.10 (1.79, 2.45)	5	3.31 (1.37, 8.00)
	Red blood cell count decreased	1508	12.83 (12.16, 13.53)	1311	14.55 (13.75, 15.40)	131	5.61 (4.72, 6.66)	59	7.69 (5.95, 9.94)	7	46.20 (21.85, 97.70)
	Hemoglobin decreased	1506	3.58 (3.40, 3.77)	1149	3.59 (3.38, 3.81)	272	3.50 (3.11, 3.95)	85	3.33 (2.69, 4.12)	0	—
	Full blood count decreased	1467	15.61 (14.78, 16.49)	1316	18.29 (17.27, 19.37)	96	5.03 (4.11, 6.15)	55	8.79 (6.74, 11.46)	0	—
Skin and subcutaneous tissue disorders	Alopecia	5523	5.31 (5.17, 5.45)	4867	6.17 (6.00, 6.35)	497	2.52 (2.31, 2.75)	154	2.38 (2.03, 2.79)	5	3.87 (1.60, 9.37)
	Rash	2282	1.10 (1.06, 1.15)	1682	1.07 (1.02, 1.13)	462	1.23 (1.12, 1.35)	137	1.11 (0.94, 1.32)	1	—
	Pruritus	1820	1.09 (1.04, 1.14)	1321	1.04 (0.99, 1.10)	433	1.43 (1.30, 1.57)	66	0.66 (0.52, 0.84)	0	—
	Dry skin	1289	1.86 (1.76, 1.97)	1060	2.02 (1.90, 2.15)	209	1.65 (1.44, 1.90)	20	0.48 (0.31, 0.75)	0	—
Blood and lymphatic system disorders	Neutropenia	4550	7.88 (7.65, 8.13)	3478	7.85 (7.58, 8.12)	899	8.22 (7.69, 8.78)	169	4.64 (3.99, 5.40)	4	5.48 (2.04, 14.68)
	Anemia	1782	2.23 (2.12, 2.33)	1255	2.06 (1.95, 2.18)	349	2.38 (2.15, 2.65)	169	3.53 (3.04, 4.11)	9	9.54 (4.92, 18.49)
	Leukopenia	1077	5.38 (5.06, 5.72)	785	5.12 (4.77, 5.50)	263	7.05 (6.24, 7.97)	29	2.35 (1.63, 3.38)	0	—
	Bone marrow failure	922	9.51 (8.89, 10.17)	896	12.20 (11.40, 13.06)	13	0.69 (0.40, 1.18)	13	2.10 (1.22, 3.62)	0	—
Nervous system disorders	Headache	2534	0.86 (0.83, 0.90)	1976	0.89 (0.85, 0.93)	444	0.83 (0.76, 0.92)	111	0.63 (0.53, 0.76)	3	0.86 (0.28, 2.67)
	Dizziness	2291	1.04 (0.99, 1.08)	1793	1.07 (1.02, 1.12)	371	0.92 (0.83, 1.02)	124	0.94 (0.79, 1.12)	3	1.14 (0.37, 3.55)
	Memory impairment	1084	1.63 (1.54, 1.73)	943	1.87 (1.76, 2.00)	119	0.98 (0.82, 1.17)	22	0.55 (0.36, 0.84)	0	—
	Neuropathy peripheral	1014	2.29 (2.15, 2.43)	941	2.80 (2.63, 2.99)	48	0.59 (0.44, 0.78)	25	0.94 (0.63, 1.39)	0	—

(Continued)

Table 3. (Continued)

SOC	PT	CDK4/6 inhibitor		Palbociclib		Ribociclib		Abemaciclib		Trilaciclib	
		N	ROR (95% CI)	*N*	ROR (95% CI)	*N*	ROR (95% CI)	*N*	ROR (95% CI)	*N*	ROR (95% CI)
Musculoskeletal and connective tissue disorders	Arthralgia	2390	1.26 (1.21, 1.31)	1976	1.38 (1.32, 1.44)	356	1.03 (0.93, 1.15)	57	0.50 (0.39, 0.65)	1	0.44 (0.06, 3.13)
	Back pain	1664	1.56 (1.49, 1.64)	1280	1.59 (1.50, 1.68)	355	1.83 (1.65, 2.04)	29	0.45 (0.32, 0.65)	0	—
	Pain in extremity	1627	1.19 (1.13, 1.25)	1236	1.19 (1.12, 1.26)	352	1.42 (1.27, 1.57)	39	0.48 (0.35, 0.65)	0	—
	Bone pain	1086	4.06 (3.82, 4.31)	845	4.14 (3.87, 4.44)	217	4.38 (3.83, 5.01)	24	1.47 (0.98, 2.19)	0	—
Respiratory, thoracic and mediastinal disorders	Dyspnea	2971	1.17 (1.13, 1.22)	2236	1.16 (1.12, 1.21)	568	1.23 (1.14, 1.34)	155	1.03 (0.88, 1.20)	12	4.07 (2.29, 7.25)
	Cough	2124	1.63 (1.56, 1.70)	1614	1.63 (1.55, 1.72)	428	1.80 (1.64, 1.98)	76	0.97 (0.78, 1.22)	6	3.88 (1.73, 8.71)
	Epistaxis	1122	3.19 (3.00, 3.38)	1012	3.79 (3.56, 4.04)	89	1.37 (1.11, 1.68)	20	0.94 (0.60, 1.45)	1	—
Infections and infestations	Pneumonia	1446	0.94 (0.89, 0.99)	1073	0.92 (0.86, 0.98)	250	0.89 (0.79, 1.01)	113	1.24 (1.03, 1.49)	10	5.58 (2.98, 10.48)
	COVID-19	1347	1.40 (1.32, 1.47)	1001	1.37 (1.29, 1.46)	259	1.48 (1.31, 1.67)	86	1.50 (1.21, 1.85)	1	—
	Nasopharyngitis	1203	1.37 (1.30, 1.45)	1025	1.55 (1.45, 1.64)	157	0.98 (0.84, 1.15)	21	0.40 (0.26, 0.61)	0	—
	Urinary tract infection	1027	1.33 (1.25, 1.42)	834	1.43 (1.33, 1.53)	141	1.00 (0.85, 1.18)	52	1.13 (0.86, 1.48)	0	—
Metabolism and nutrition disorders	Decreased appetite	3296	3.12 (3.01, 3.23)	2553	3.18 (3.06, 3.31)	460	2.36 (2.15, 2.58)	282	4.44 (3.95, 5.00)	1	—
	Dehydration	1040	1.93 (1.81, 2.05)	653	1.59 (1.47, 1.72)	132	1.34 (1.13, 1.59)	254	7.98 (7.05, 9.03)	1	—
Psychiatric disorders	Insomnia	1290	1.09 (1.03, 1.15)	1048	1.17 (1.10, 1.24)	206	0.96 (0.83, 1.10)	36	0.51 (0.37, 0.71)	0	—
	Anxiety	874	0.68 (0.64, 0.73)	673	0.69 (0.64, 0.75)	176	0.76 (0.65, 0.88)	19	0.25 (0.16, 0.39)	6	3.99 (1.78, 8.95)
Vascular disorders	Hot flush	1500	4.80 (4.55, 5.05)	1325	5.58 (5.28, 5.90)	138	2.35 (1.99, 2.78)	37	1.92 (1.39, 2.66)	0	—

CDK4/6, cyclin-dependent kinases 4 and 6; FAERS, Food and Drug Administration Adverse Event Reporting System; ROR, reporting odds ratio; SOC, system organ class.

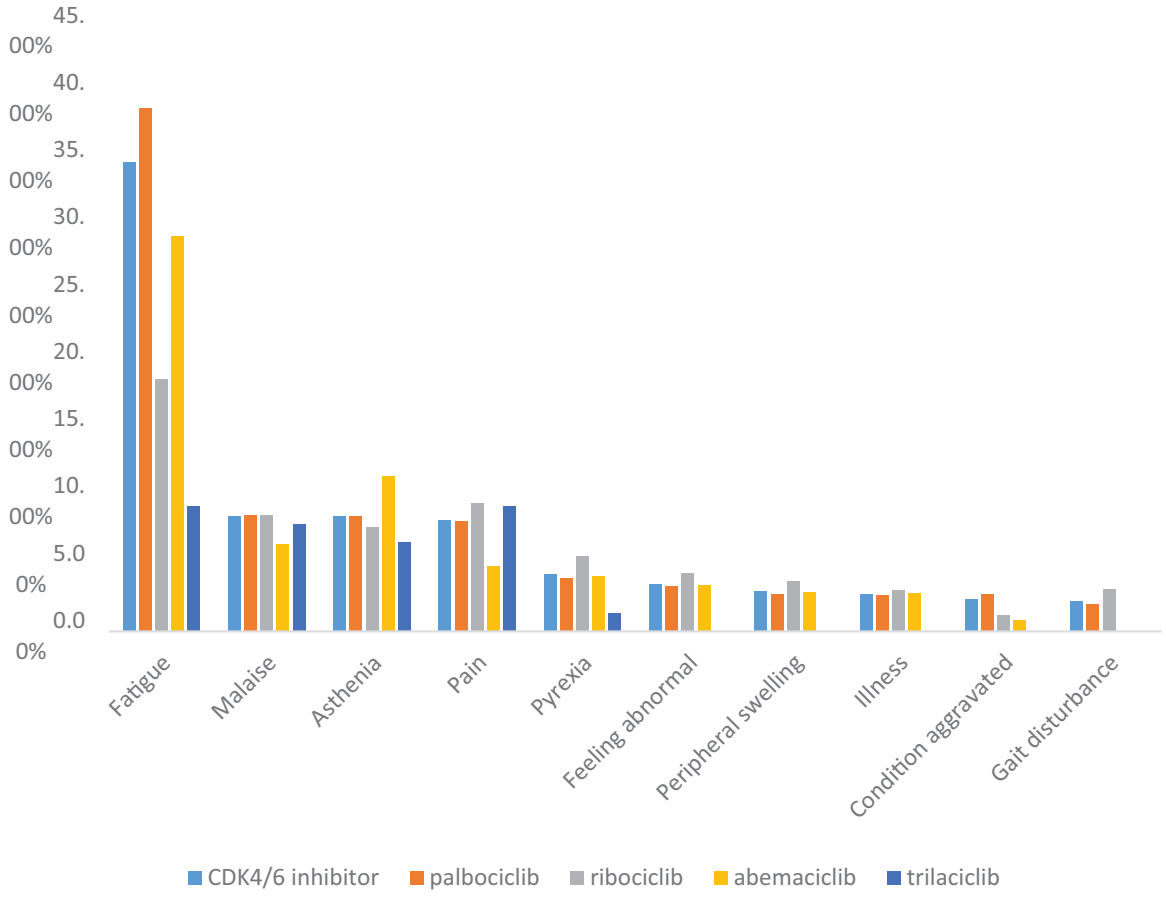

Figure 2. The top 10 adverse events for general disorders and administration site conditions.

Investigations, blood, and lymphatic system disorders. In accordance with the SMQs, we compiled a comprehensive dataset, detailed in Supplemental Table S4, containing the frequency of AE reports and their respective RORs with respect to PTs associated with hematopoietic cytopenias. Notably, compared to abemaciclib, ribociclib and palbociclib showed a significant signal among the PTs in this category. For example, decreased white blood cell count ($n=8899$, ROR = 28.10), abnormal complete blood count ($n=2052$,ROR = 19.55), decreased neutrophil count ($n=1594$, ROR = 12.95), decreased complete blood count ($n=1316$, ROR = 18.29), decreased red blood cell count ($n=1311$, ROR = 14.55), and bone marrow failure ($n=896$, ROR = 12.20).

Figure 4 was constructed to illustrate the 10 most frequently reported hematopoietic cytopenias in relation to PTs. In this SMQ, the most common AEs associated with palbociclib were decreased white blood cell count, neutropenia, and abnormal complete blood count. For ribociclib, the most common AEs were neutropenia, decreased white blood cell count, and anemia. In contrast, abemaciclib seemed to have a lower rate of reduced white blood cell counts and abnormal complete blood counts, while exhibiting a higher rate of decreased platelet counts and anemia.

Other SOCs. In addition, analysis of AE data revealed notable signals associated with CDK4/6 inhibitors. Specifically, CDK4/6 inhibitors showed robust associations with alopecia ($n=5523$, ROR = 5.31), hot flush ($n=1500$, ROR = 4.80), bone pain ($n=1086$, ROR = 4.06), and epistaxis ($n=1122$, ROR = 3.19).

In contrast, abemaciclib demonstrated comparatively fewer reports and lower RORs for these AEs in the same patient population, namely alopecia ($n=154$, ROR = 2.38), hot flush ($n=37$, ROR = 1.92), bone pain ($n=24$, ROR = 1.47),

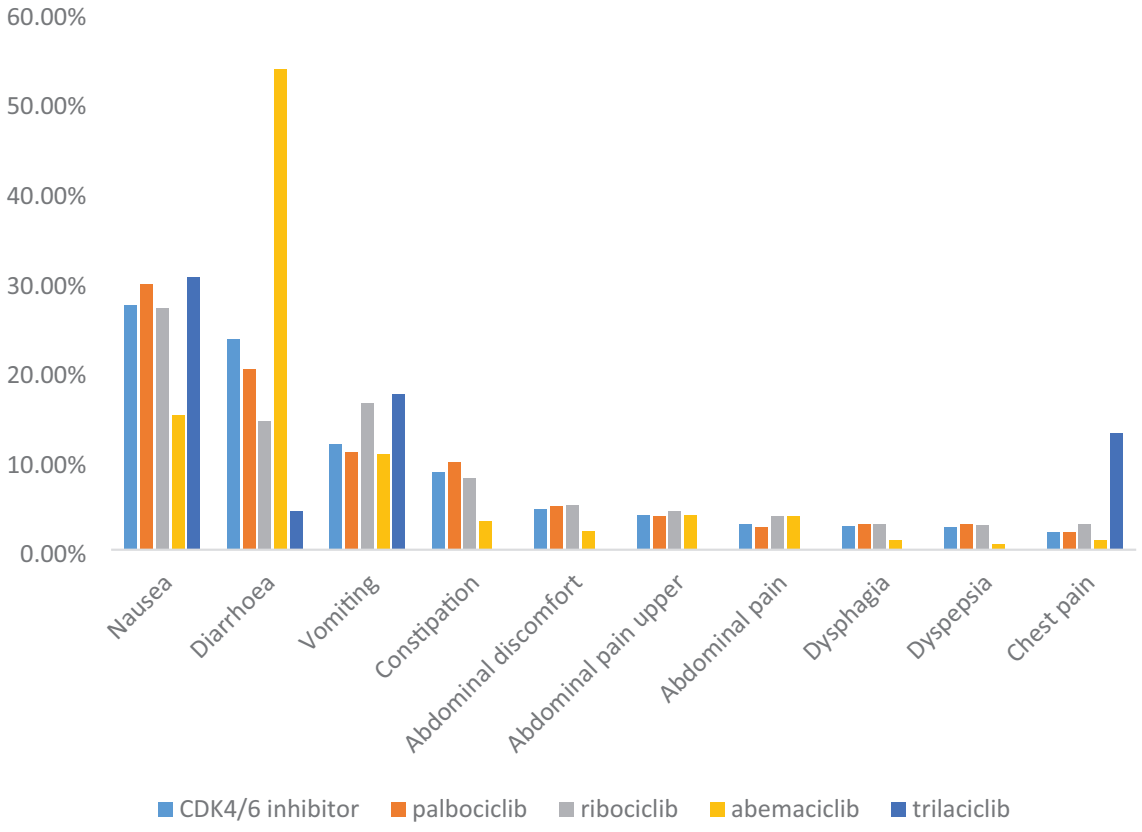

Figure 3. The top 10 adverse events for gastrointestinal nonspecific inflammation and dysfunctional conditions.

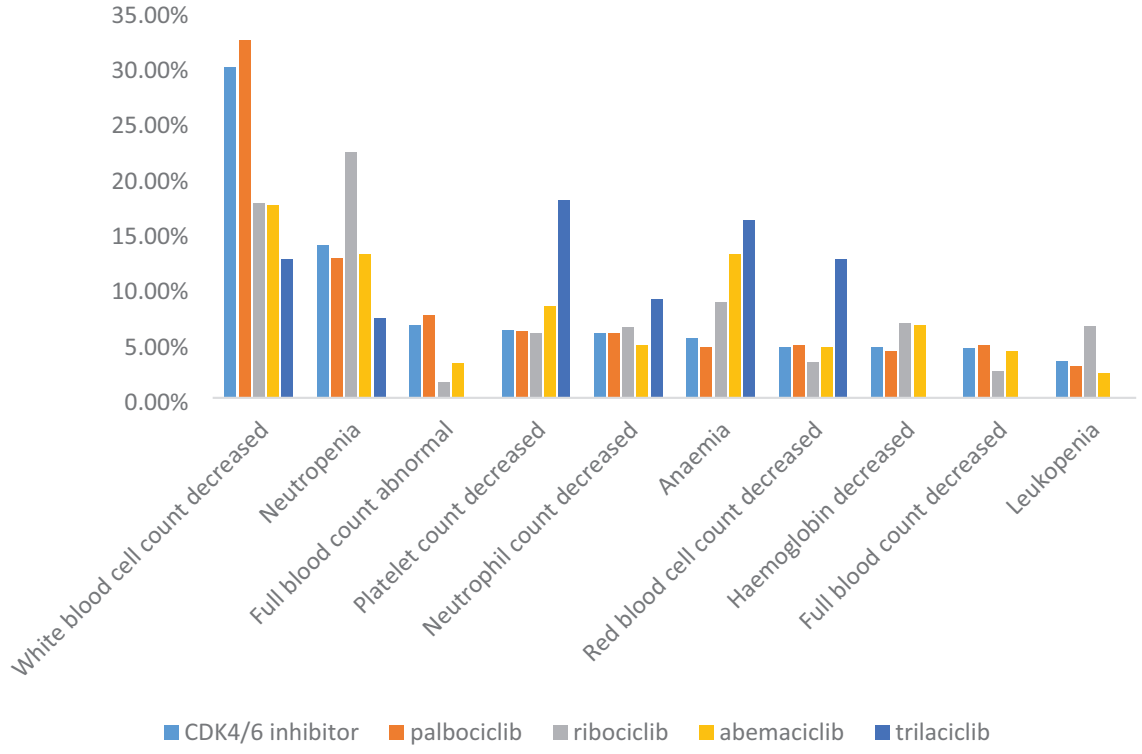

Figure 4. The top 10 AEs for hematopoietic cytopenias-related AEs.
AE, adverse events.

and epistaxis ($n = 20$, ROR = 0.94). Notably, abemaciclib exhibited significant signals for decreased appetite ($n = 282$, ROR = 4.44) and dehydration ($n = 254$, ROR = 7.98). Comprehensive details are provided in Table 3 for reference and further analysis.

Novel safety signals and sensitivity analysis

From these data, we found that the SOC "psychiatric disorders" contained several PTs with positive novel signals that were not listed in the drug labels. These included stress, eating disorders, depressed mood, nervousness, and emotional disorders. We also identified a category of nail-related AEs, such as nail disorder, onychoclasis, and nail discoloration, as novel signals (see Supplemental Table S5).

In response to the aforementioned new signals, we conducted a sensitivity analysis, excluding the impact of AEs associated with concomitant drug use. Following the sensitivity analysis, three novel signals (depressed mood, nervousness, and stress) from ROR analysis were found to be nonsignificant. The other new signals associated with CDK4/6 inhibitors, namely onychoclasis, nail disorder, and nail discoloration, and psychiatric disorders signals such as eating disorder and emotional disorder were still robust.

Discussion

Due to the limitations of pre-marketing trials, such as small sample size and short duration of medication, it is difficult to find some delayed or rare adverse reactions.[25] However, to some extent, the lack of clinical drug safety information can be compensated by mining the FAERS database. In this study, the AE reports from FAERS were analyzed and all signals were captured by the ROR mining method. Subsequently, validation was conducted using PRR and BCPNN. ROR included almost all positive signals identified by both PRR and BCPNN. The results showed that some adverse reactions involved in the drug label were essentially included in the signal list, such as diarrhea, nausea, fatigue, vomiting, loss of appetite, dehydration, etc., and most of them were also ranked high, which improved the reliability of this study.

In the FAERS database, there are significant differences in AE data between different drugs, which are largely influenced by factors such as the drug's market launch date, market region, and sales volume. In the CDK4/6 data we obtained, the number of AEs is correlated with the year of launch. The drug with the highest number of data points is palbociclib, with 212,350 reports, mainly because it was launched earliest. Dalpiciclib was launched in China on December 31, 2021, and currently, no PS-related data have been retrieved from FAERS for it. We examined the annual trend of the total reports; the overall annual trend initially showed a gradual increase, but palbociclib experienced a decrease in 2021, followed by a general increase (see Supplemental Figure S2). This trend may be related to the sales volume of the drug, as the sales of palbociclib started to decline in 2021, while the sales of other drugs increased year by year.

Several FAERS analyses pertaining to CDK4/6 inhibitors have concentrated on AEs of particular interest or specific occurrences. For instance, Raschi[23] delved into the association between skin toxicities and CDK4/6 inhibitors, while Yan et al.[29] explored the relationship between thromboembolic events and CDK4/6 inhibitors. Additionally, Nawa et al.[30] investigated the connection between lung disease and CDK4/6 inhibitors. In our study, these AEs were also considered positive signals.

Palbociclib showed a significant signal in this category, with decreased white blood cell count being the most commonly reported AE. Ribociclib also shows some association with decreased white blood cell count and neutropenia. In contrast, abemaciclib appears to have a lower incidence of these specific AEs but a higher incidence of decreased platelet count and anemia. These differences may influence the choice of CDK4/6 inhibitor based on a patient's hematologic profile. Moreover, some latest research works[31–33] suggested that it was crucial to consider additional factors such as BMI and specific polymorphisms that affect absorption, distribution, metabolism and excretion (ADME) genes, which may provide a comprehensive understanding of the factors influencing CDK4/6 inhibitor efficacy and safety.

The analysis also revealed additional AEs that may not fit into the previous categories. In particular, alopecia, hot flush, bone pain, and epistaxis have been associated with CDK4/6 inhibitors, with palbociclib showing the strongest

signals. In contract, abemaciclib had fewer reports and lower relative odds of these AEs. Instead, it was more strongly associated with decreased appetite and dehydration. In clinical practice, these findings provide valuable insight for healthcare providers when selecting a CDK4/6 inhibitor for a specific patient. Factors such as the patient's tolerability to AEs, pre-existing medical conditions, and individual response to treatment may influence the choice of medication. For example, a patient with a history of gastrointestinal issues may be better suited to a CDK4/6 inhibitor that is less associated with diarrhea, while a patient with pre-existing anemia may need to consider the hematopoietic cytopenias profile of each drug.

Interestingly, we identified some AEs that have not been previously mentioned in clinical trials or real-world case reports, nail-related disorders, including onychoclasis, nail disorder, and nail discoloration. These were completely new AE signals discovered in this study. In our literature search, we found that other targeted cancer therapies can also cause nail-related side effects, more commonly observed with drugs such as sunitinib and sorafenib.[34,35] The mechanism may involve interference with the normal nail growth process or weakening of the nail structure. Side effects of CDK4/6 inhibitors may include nail-related problems as a secondary effect, such as changes in blood circulation that could affect nail health. Anticancer drugs like palbociclib can sometimes interfere with the nutrient's absorption or metabolism in the body. Nutritional deficiencies, particularly in vitamins and minerals important for nail health (e.g., biotin), may contribute to onychoclasis. Palbociclib may potentially weaken the nails, making them more likely to break or split. This weakening may occur at the cellular or molecular level.

Another category of AEs that was rarely reported in clinical practice was psychiatric disorders. Some typical examples were depressed mood, nervousness, stress, emotional disorders and eating disorders. However, the three former AEs were not signals after sensitivity analysis, which meant that although the CDK4/6 inhibitors were considered PS drugs in FAERS database, the concomitant drugs such as zolpidem, lorazepam, etc. may have more likely contributed to these AEs. Nevertheless, our findings suggest that there may be an increased risk of developing these events in patients taking CDK4/6 inhibitors. These AEs related to mental health were not commonly reported but are important for healthcare providers to be aware of when prescribing or monitoring these medications.

Furthermore, several frequently reported AEs listed in the drug label almost showed significant signals. Although the data for trilaciclib were limited, we did observe notable differences compared to the other three drugs. However, due to the small amount of data available, a comprehensive study and discussion was not pursued.

The present study has several limitations that need to be addressed. First, given the limitations of the FAERS database, we could not estimate the incidence rate of each AE. Data mining from the FAERS database fails to provide sufficient evidence on causality between AEs and drugs. In addition, we removed some reports that were not directly related to drugs; however, a few AEs unrelated to CDK4/6 inhibitors may have remained.

Conclusion

Several key findings emerged from the analysis of AEs associated with CDK4/6 inhibitors. Palbociclib and ribociclib had similar safety profiles with some differences, while abemaciclib stood out with a unique pattern of AEs. Commonly reported AEs included gastrointestinal issues such as nausea, diarrhea, vomiting, and constipation, along with hematopoietic cytopenias such as decreased white blood cell count and neutropenia. Notably, new AE signals with CDK4/6 inhibitors were psychiatric concerns such as eating disorders and emotional disorders and nail disorders including onychoclasis, nail disorder, and nail discoloration.

In conclusion, CDK4/6 inhibitors have a distinct AE profile that requires careful patient monitoring. Healthcare providers should be aware of potential mental health and nail-related AEs and weigh the risks and benefits when making decisions regarding the use CDK4/6 inhibitors.

Declarations

Ethics approval and consent to participate

Ethics approval and consent were not required for our research, because our research was conducted using legally obtained public data—FAERS data,

which can be freely accessed on the FDA website, all participant data were anonymized by the FDA and in accordance with the ethical standard. Our research did not involve any treatment intervention or interfere with public behavior.

Consent for publication
Not applicable.

Author contributions
Jun Shen: Data curation; Resources; Writing – original draft; Writing – review & editing.

Pingli Luo: Investigation; Methodology; Software.

Jianmei Xu: Supervision; Validation; Writing – review & editing.

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Competing interests
The authors declare that there is no conflict of interest.

Availability of data and materials
Datasets from FAERS we used in this research can be available publicly at: https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html

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Supplemental material
Supplemental material for this article is available online.

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