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Research article

# A real-world disproportionality analysis of FDA adverse event reporting system (FAERS) events for alpelisib

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ABSTRACT

In this study, we delved into the safety profile of alpelisib, an FDA-approved treatment for hormone receptor-positive, HER2-negative, PIK3CA-mutated advanced or metastatic breast cancer, and PIK3CA-Related Overgrowth Spectrum (PROS). Despite its approval, real-world, long-term safety data is lacking. Our research scrutinizes the FDA database to assess alpelisib 's safety. We retrospectively analyzed data from April 2019 to June 2023 using four algorithms. Among 7,609,450 reports, 6692 implicated alpelisib as the primary suspected drug, uncovering adverse events (AEs) across 26 organ systems. Notably, we identified 21 previously unlisted AEs. Furthermore, differences in AEs emerged between patients with PIK3CA-mutated breast cancer and those with PROS. This study provides vital insights for healthcare professionals to navigate AEs in clinical practice and informs future research for enhancing alpelisib 's safety profile.

## 1. Introduction

Alpelisib, a highly selective α-specific inhibitor of phosphatidylinositol 3-kinases (PI3K), shows a remarkable 50-fold preference for inhibiting the p110α isoform over others [1]. This specificity is particularly relevant given that mutations in the PIK3CA gene drive PI3K-p110α activation, and Alpelisib emerges as an effective treatment for conditions linked to PIK3CA mutations [2,3]. Its Food and Drug Administration (FDA) approval in May 2019 was a pivotal moment, introducing it as the first treatment for hormone receptor (HR)-positive, HER2-negative, PIK3CA-mutated advanced or metastatic breast cancer and PIK3CA-Related Overgrowth Spectrum (PROS) [4,5]. Clinical practice has since validated alpelisib's efficacy and safety, solidifying its role in treatment strategies [6–8].

The widespread use of alpelisib after FDA approval has brought attention to its real-world adverse events (AEs). The FDA's prescribing information lists common AEs such as changes in glucose and creatinine levels, diarrhea, rash, lymphocyte count reductions, and more. Subsequent safety trials have underscored these AEs, advocating for early detection and intervention strategies, including dose adjustments, to mitigate toxicity [9]. However, patient responses can vary widely due to unique health conditions and other

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factors.

The limitations of clinical trials, such as small sample sizes and short observation periods, highlight the need for extensive post-marketing safety research in real-world settings [10]. Data from these settings are crucial for understanding the safety profile of alpelisib across diverse patient populations. Despite this, there is a notable lack of comprehensive studies focusing on alpelisib's real-world AEs.

Alpelisib is FDA-approved for two distinct conditions, PROS and PIK3CA-mutated breast cancer. These conditions differ in epidemiology and clinical presentation, and so does the prescribed alpelisib dosage for each [11]. Therefore, the AEs can vary significantly based on the indication, making it essential to study AEs in real-world contexts for each indication.

The FDA Adverse Event Reporting System (FAERS) is a key public database for post-marketing drug safety monitoring [12]. In recent years, more and more drug safety profile studies based on FAERS have been published, which shown that validity of the database and data obtained by FAERS has been recognized. Through comprehensive evaluation and scrutiny, our study investigated the disproportionality of reported AEs linked with alpelisib. This analysis revealed AEs that might have been undetected prior to FDA approval. Such data is invaluable for guiding careful alpelisib use in clinical settings and spurring further, more comprehensive research.

## 2. Methods

The FAERS database operates as a pivotal Spontaneous Reporting System (SRS), methodically aggregating global reports of AEs to fortify the FDA's post-market surveillance endeavors subsequent to the introduction of drugs and biotherapy products [13]. This system assumes a critical role in discerning and evaluating potential signals, concurrently quantifying the associations between particular drugs and the AEs documented by individuals. The database undergoes quarterly updates, encompassing an extensive spectrum of AE accounts, documentation of medication mishaps, and instances of product quality grievances.

### 2.1. Data sources and procedures

In this study, our primary focus was on extracting and scrutinizing pertinent reports related to alpelisib from the FAERS database, available at https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html. The FAERS data package is presented as a zipped package on the website. The data file has seven sections containing demographic and management information, drug information, AEs, patient outcomes, reporting sources, starting and ending dates of treatment with reported drugs, indications, and deleted cases. We compiled data from the drug's initial FDA approval in the second quarter of 2019 up to the latest available data in the second quarter of 2023. However, given the potential for duplicated entries in the FAERS database, a thorough deduplication process was undertaken.

AEs recorded in the FAERS database underwent a comprehensive coding process using the Medical Dictionary for Regulatory Activities 26.0 (MedDRA 26.0). To effectively categorize these events, the hierarchical structure of the MedDRA terminology was strategically organized into five distinct levels: system organ class (SOC), high-level group term (HLGT), high-level term (HLT), preferred term (PT), and lowest-level term (LLT). Our specific focus within this study was to capture all AEs associated with alpelisib, a specific drug, as outlined in the REAC files meticulously curated within the FAERS database. This approach enabled us to systematically identify and isolate these events, subsequently allowing for a detailed analysis of their frequency and severity. This analysis was conducted using MedDRA classifications, both at the broader SOC level and the more detailed PT level.

In the context of characterizing AEs within drug-related reports, the responsibility of assigning these codes lies with the individuals reporting the events. The potential codes available for assignment were: 1 = suspect, 2 = concomitant, and 3 = interacting. In order to enhance the precision and accuracy of our analysis, we opted to designate the code "1″ as "PS" (primary suspected) within the DRUG files. This strategic decision was made to elevate the accuracy of our analysis and overall conclusions.

### 2.2. Statistical analysis

Disproportionality analysis is a crucial technique in pharmacovigilance studies, playing a vital role in identifying potential signals indicating AEs associated with a drug [14]. This methodology involves a comparative assessment of the frequency of AEs linked to a specific drug against the occurrence of AEs related to all other medications. Fundamentally, it relies on the concept that a signal emerges during data extraction when the incidence rate of a particular AE for a given drug significantly surpasses the background occurrence rate observed across the entire database. This deviation from the norm must exceed a predetermined threshold or set of criteria to be considered statistically significant.

In our analysis, we employed both Frequentist and Bayesian methodologies in the framework of disproportionality analysis. This dual approach enabled us to explore the intricate relationship between a drug and a specific AE. This exploration was facilitated through the application of several essential metrics, including the reporting odds ratio (ROR), the proportional reporting ratio (PRR), the Bayesian confidence propagation neural network (BCPNN), and the multi-item gamma Poisson shrinker (MGPS) [15]. In our study, the identification of AE signals required meeting the criteria stipulated by all four algorithms simultaneously. For a detailed understanding of the mathematical equations and criteria governing each of these algorithms, we refer readers to Supplementary Table S1. All measures of disproportionality are based on the same principles of calculation using the 2 × 2 table, as presented in Supplementary Table S2.

In our study, stratified analysis was also employed as a key methodological approach. This process entailed dividing the dataset into distinct subsets based on predefined criteria such as indications, gender, age, and the concurrent use of medications. We then

conducted separate analyses within each subset. This allowed for an in-depth examination of patterns and variations specific to each group, facilitating a comprehensive understanding of the data that might be obscured in a broader analysis.

## 3. Results

### 3.1. Characteristics of AE reports

Throughout the course of the study, a total of 7,609,450 AE reports were initially scrutinized. Following a meticulous elimination of duplicate entries, a refined dataset of 6692 reports directly associated with alpelisib remained, as depicted in Fig. 1.

To shed light on the essential traits of patients experiencing AEs specifically linked to alpelisib, a concise compilation of their fundamental characteristics was meticulously presented in Table 1. Apart from a reported number of 899 in the first and second quarters of 2023, the largest number of AE reports reached 1752 in the year 2022. This was closely followed by the year 2021, recording 1686. Of the patients who experienced AEs associated with alpelisib collected from FAERS, AEs occurred mainly in female (n = 5814 , 95.64%), adult (n = 2,367, 96.86%) and breast cancer emerges as the predominant indicated condition (n = 2,971, 81.53%). Among the serious outcomes documented, hospitalization stood at the forefront (n = 1,225, 34.80%), followed by cases culminating in fatality (n = 945, 26.85%). Our exploration of the top five combination drugs associated with alpelisib-related AEs led us to identify fulvestrant, metformin, faslodex, letrozole, and ribociclib as the primary contenders in this regard.

### 3.2. Disproportionality analysis

The signal reports for alpelisib at the SOC level are presented in Table 2. AE occurrences linked to alpelisib encompass a wide spectrum of 26 distinct organ systems. Among these, “General disorders and administration site conditions (SOC: 10018065, n = 2770)", “Gastrointestinal disorders (SOC: 10017947, n = 2263)" and “Metabolism and nutrition disorders (SOC: 10027433, n = 2053)" emerged more reported number. The latter two exhibited a positive signal detection through the ROR, Information Component (IC),

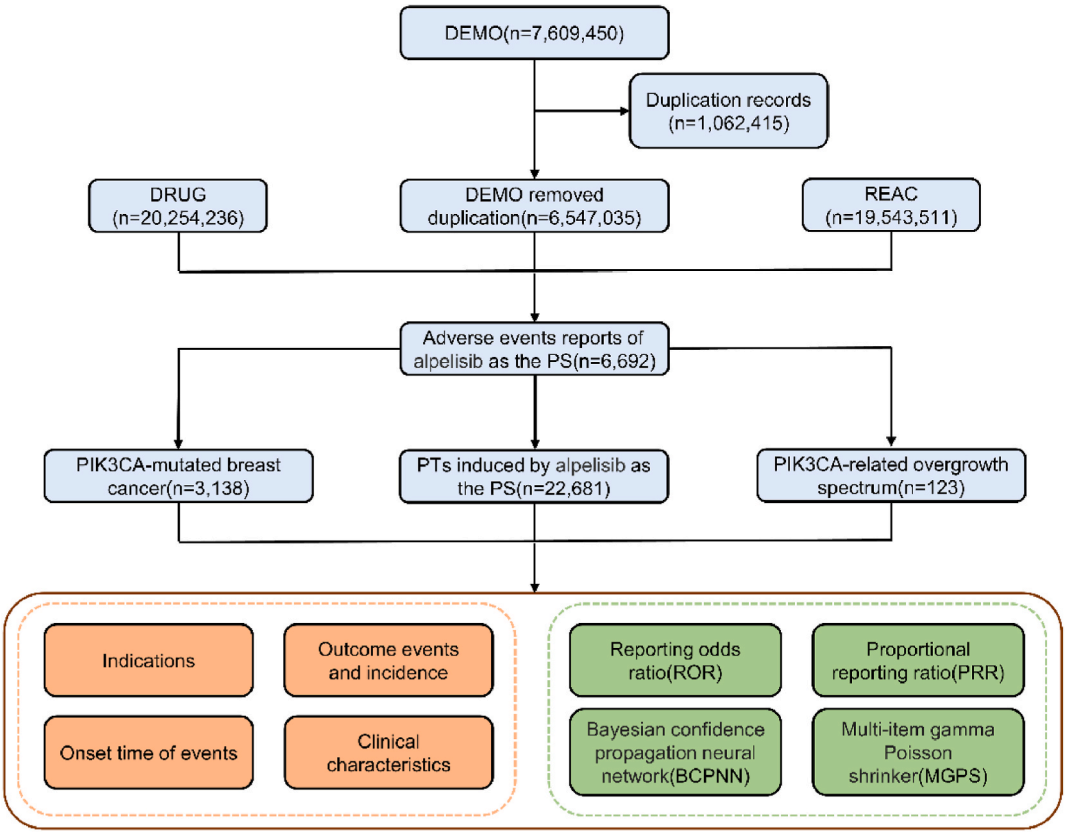


**Fig. 1.** The flow diagram of selecting alpelisib-related AEs from FAERS database
DEMO: demographic file
DRUG: drug file
REAC: reaction file
PS: primary suspect

**Table 1**
Clinical characteristics of reports with alpelisib from the FAERS database (April 2019 to June 2023).

| Characteristics | Alpelisib-induced AE reports (n = 6692) | | |
|---|---|---|---|
| Number of events | Available number | Case number | Case proportion |
| Gender, n (%) | 6079 | – | 90.84% |
| Female | – | 5814 | 95.64% |
| Male | – | 265 | 4.36% |
| Age (years), n (%) | 2392 | – | 35.74% |
| <18 | – | 75 | 3.14% |
| 18 ≤ and ≤65 | – | 1277 | 53.39% |
| >65 | – | 1090 | 45.57% |
| Median (IQR) | – | 63 (54–71) | – |
| Weight (Kg), n (%) | 877 | – | 13.11% |
| <80 | – | 686 | 78.22% |
| 80 ≤ and ≤100 | – | 137 | 15.62% |
| >100 | – | 54 | 6.16% |
| Median (IQR) | – | 65.74 (55.8–76.95) | – |
| Reported countries, n (%) | 6692 | – | 100.00% |
| US | – | 5410 | 80.84% |
| Non-US | – | 1282 | 19.16% |
| Indications, n (%) | 3644 | – | 54.45% |
| Breast cancer | – | 1627 | 44.65% |
| Breast cancer metastatic | | 939 | 25.77% |
| Breast cancer female | | 405 | 11.11% |
| Pik3ca related overgrowth spectrum | – | 123 | 3.38% |
| Pik3ca-activated mutation | – | 100 | 2.74% |
| Others | – | 450 | 12.35% |
| Combination drugs, n (%) | 1931 | – | 28.86% |
| Fulvestrant | – | 619 | 32.06% |
| Metformin | – | 217 | 11.24% |
| Faslodex | – | 217 | 11.24% |
| Letrozole | – | 181 | 9.37% |
| Kisqali | – | 126 | 6.53% |
| Outcomes, n (%) | 6692 | – | 100.00% |
| Non-serious Outcome | – | 3172 | 47.40% |
| Serious Outcome | – | 3520 | 52.60% |
| Death | – | 945 | 26.85% |
| Life-threatening | – | 126 | 3.58% |
| Hospitalization | – | 1225 | 34.80% |
| Disability | – | 10 | 0.28% |
| Other serious outcomes | – | 1884 | 53.52% |
| Time-to-onset (days) | 631 | | 9.43% |
| Median (IQR) | | 20 (7–66) | |
| Reporters, n (%) | 6334 | – | 94.65% |
| Health professional | – | 3178 | 50.17% |
| Consumer | – | 3156 | 49.83% |
| Reporting year, n (%) | 6692 | – | 100.00% |
| 2023Q1-Q2 | – | 899 | 13.43% |
| 2022 | – | 1752 | 26.18% |
| 2021 | – | 1686 | 25.19% |
| 2020 | – | 1653 | 24.70% |
| 2019Q2-Q4 | – | 702 | 10.49% |

and Empirical Bayes Geometric Mean (EBGM) methods. However, the SOC labeled as "General disorders and administration site conditions (SOC: 10018065, n = 2770)" demonstrated a positive signal using the ROR and IC methods, while this wasn't mirrored in the Proportional PRR and EBGM methods.

Additionally, we conducted disproportionality analysis at the PT, as presented in Supplementary Table S3. Not only that, based on the disproportionality analysis of PT, we further conducted analysis at gender, age, and whether concomitant drugs were used, as presented in Supplementary Table S4. And we had statistics on the Time-to-onset of AEs, which are presented in Supplementary Table S5.

In addition to the adverse drug reactions cataloged by the FDA, our study has unveiled a collection of unexpected AEs, including lip swelling, reflux gastritis, diverticulum intestinal, intra-abdominal fluid collection, tongue discomfort, bacteriuria, laryngitis viral, vulvovaginal candidiasis, blood chloride decreased, coma hepatic, feeding disorder, eating disorder, parosmia, cervix disorder, rectocele, allergic sinusitis, polyuria, pleural effusion, nail cuticle fissure, onychoclasis, and lymphoedema.

### *3.3. Characteristics of AE reports for different indications*

Separate analyses for each indication were detailed in Table 3. Upon comparison of the overall clinical profiles between these two

**Table 2**
Signal strength of reports of alpelisib at the System Organ Class (SOC) level in FAERS database.

| SOC | | Case number(n) | ROR (95%two-sided CI)) | PRR (χ2) | IC (IC025) | EBGM (EBGM05) |
|---|---|---|---|---|---|---|
| General disorders and administration site conditions | 2770 | 1.01 (0.97–1.05) | 1.01 (0.34) | 69.18 (66.40) | 1.01 (0.97) | |
| Gastrointestinal disorders | 2263 | 2.30 (2.20–2.40) | 2.11 (1415.40) | 0.93 (0.89) | 2.11 (2.02) | |
| **Metabolism and nutrition disorders** | **2053** | **6.49 (6.20–6.80)** | **5.78 (8247.25)** | **0.40 (0.38)** | **5.75 (5.49)** | |
| Investigations | 1711 | 2.10 (2.00–2.21) | 1.98 (879.96) | 1.01 (0.96) | 1.98 (1.88) | |
| Skin and subcutaneous tissue disorders | 1681 | 2.11 (2.00–2.22) | 1.99 (871.50) | 1.01 (0.96) | 1.99 (1.89) | |
| Nervous system disorders | 770 | 0.67 (0.62–0.72) | 0.69 (119.93) | −1.83 (−1.97) | 0.69 (0.64) | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 689 | 0.90 (0.83–0.97) | 0.90 (7.99) | −6.61 (−7.13) | 0.90 (0.83) | |
| Injury, poisoning and procedural complications | 645 | 0.31 (0.28–0.33) | 0.33 (975.83) | −0.63 (−0.68) | 0.33 (0.31) | |
| Infections and infestations | 495 | 0.54 (0.49–0.59) | 0.55 (190.64) | −1.17 (−1.28) | 0.55 (0.51) | |
| Respiratory, thoracic and mediastinal disorders | 460 | 0.68 (0.62–0.75) | 0.69 (65.25) | −1.89 (−2.08) | 0.69 (0.63) | |
| Musculoskeletal and connective tissue disorders | 399 | 0.57 (0.51–0.63) | 0.58 (127.70) | −1.27 (−1.40) | 0.58 (0.52) | |
| Psychiatric disorders | 311 | 0.41 (0.37–0.46) | 0.42 (260.68) | −0.80 (−0.90) | 0.42 (0.38) | |
| Renal and urinary disorders | 246 | 0.75 (0.66–0.85) | 0.75 (20.59) | −2.43 (−2.76) | 0.75 (0.66) | |
| Immune system disorders | 188 | 0.75 (0.65–0.87) | 0.75 (15.23) | −2.46 (−2.85) | 0.75 (0.65) | |
| Eye disorders | 185 | 0.65 (0.56–0.75) | 0.65 (34.50) | −1.63 (−1.89) | 0.65 (0.57) | |
| Vascular disorders | 183 | 0.48 (0.42–0.56) | 0.49 (100.92) | −0.97 (−1.12) | 0.49 (0.42) | |
| Blood and lymphatic system disorders | 153 | 0.51 (0.43–0.59) | 0.51 (72.96) | −1.03 (−1.21) | 0.51 (0.44) | |
| Surgical and medical procedures | 146 | 0.51 (0.44–0.60) | 0.52 (66.46) | −1.06 (−1.24) | 0.52 (0.44) | |
| Hepatobiliary disorders | 132 | 0.88 (0.74–1.05) | 0.88 (2.04) | −5.61 (−6.65) | 0.88 (0.74) | |
| Product issues | 78 | 0.23 (0.18–0.28) | 0.23 (203.21) | −0.47 (−0.59) | 0.23 (0.19) | |
| Cardiac disorders | 75 | 0.21 (0.17–0.27) | 0.22 (218.34) | −0.45 (−0.57) | 0.22 (0.17) | |
| Reproductive system and breast disorders | 59 | 0.51 (0.39–0.66) | 0.51 (28.04) | −1.03 (−1.33) | 0.51 (0.39) | |
| Congenital, familial and genetic disorders | 40 | 0.92 (0.67–1.25) | 0.92 (0.31) | −7.92 (−10.81) | 0.92 (0.67) | |
| Ear and labyrinth disorders | 34 | 0.42 (0.30–0.58) | 0.42 (27.62) | −0.80 (−1.11) | 0.42 (0.30) | |
| Endocrine disorders | 11 | 0.21 (0.12–0.39) | 0.21 (31.91) | −0.45 (−0.81) | 0.21 (0.12) | |
| Social circumstances | 11 | 0.11 (0.06–0.21) | 0.11 (75.72) | −0.32 (−0.58) | 0.11 (0.06) | |

SOC, system organ class; PT, preferred term; ROR, reporting odds ratio; CI, confidence interval; PRR, proportional reporting ratio; χ2, chi-information component; IC, information component; IC025, the lower limit of 95% CI of the IC; EBGM, empirical Bayesian geometric mean; EBGM05, the lower limit of 95% CI of EBGM.

groups, significant disparities emerged in terms of gender distribution, age distribution, weight, and the incidence of severe outcomes. In both groups, the number of female patients far exceeded that of males. However, when it came to age, the median value for the PROS group (14 years) was markedly lower than that for the PIK3CA-mutated breast cancer group (63 years). We further examined outcome indicators for all patients. The death toll was more for the PIK3CA-mutated breast cancer group (n = 390) compared to the PROS group (n = 0). The population of life-threatening was more for the PROS group (n = 75) than for the PIK3CA-mutated breast cancer group (n = 4).

**Table 3**
Clinical information associated with specific indications.

| | PIK3CA-mutated breast cancer | PIK3CA-related overgrowth spectrum |
|---|---|---|
| Total | 3138 | 123 |
| Gender, n (%) | – | – |
| Female | 2938 (98.76%) | 66 (61.68%) |
| Male | 37 (1.24%) | 41 (38.32%) |
| Age (years), n (%) | – | – |
| <18 | 1 (0.07%) | 49 (58.33%) |
| 18 ≤ and ≤65 | 797 (53.71%) | 34 (40.48%) |
| >65 | 686 (46.23%) | 1 (1.19%) |
| Median (IQR) | 63(55–71) | 14(7–28) |
| Weight (Kg), n (%) | – | – |
| <80 | 487 (78.17%) | 29 (74.36%) |
| 80 ≤ and ≤100 | 92 (14.77%) | 7 (17.95%) |
| >100 | 44 (7.06%) | 3 (7.69%) |
| Median (IQR) | 66.68 (56.1–76.72) | 56.4 (40–80) |
| Reported countries, n (%) | – | – |
| US | 2009 (64.02%) | 94 (76.42%) |
| Other country | 1129 (35.98%) | 29 (23.58%) |
| Outcomes, n (%) | – | – |
| Non-serious Outcome | 1191 (37.95%) | 70 (56.91%) |
| Serious Outcome | 1947 (62.05%) | 53 (43.09%) |
| Death | 390 (20.03%) | 0 (0.00%) |
| Life-threatening | 75 (3.85%) | 4 (7.55%) |
| Hospitalization | 780 (40.06%) | 24 (45.28%) |
| Disability | 26 (1.34%) | 1 (1.89%) |
| Other serious outcomes | 1128 (57.94%) | 38 (71.70%) |
| Time-to-onset (days) | 415 (13.22%) | 37 (30.08%) |
| Median (IQR) | 21 (9–68) | 5 (0–75) |
| Reporters, n (%) | – | – |
| Health professional | 1813 (60.21%) | 68 (55.28%) |
| Consumer | 1198 (39.79%) | 55 (44.72%) |
| Reporting year, n (%) | – | – |
| 2023Q1-Q2 | 432 (13.77%) | 66 (53.66%) |
| 2022 | 888 (28.30%) | 40 (32.52%) |
| 2021 | 914 (29.13%) | 14 (11.38%) |
| 2020 | 587 (18.71%) | 3 (2.44%) |
| 2019Q2-Q4 | 317 (10.10%) | 0 (0.00%) |

### *3.4. Adverse reaction frequency analysis*

PTs related to different indications of alpelisib were excluded from the analysis and then ranked in descending order based on their frequency and ROR. Table 4 presents the top significant safety signals individually. We then conducted a comparison with the adverse reactions specified in the drug instructions, using an asterisk (*) to denote those not mentioned in the instructions.

## 4. Discussion

Drawing upon the extensive dataset within the FAERS database, our study offers a comprehensive analysis of the real-world safety profile of alpelisib. According to the characteristics of AE reports, an upward trajectory emerges in the number of reported AEs in FAERS as the years progress, which may be related to the increase in the number of patients treated by alpelisib. Given alpelisib's primary application in the treatment of advanced breast cancer, it follows that a greater number of AE reports in FAERS pertains to adult females. However, due to the absence of accurate patient numbers using alpelisib, it remain further study that which groups of patients are more likely to have AEs.

The findings of our study underscore a clustering of common SOCs around gastrointestinal disorders, metabolism and nutrition disorders, investigations, as well as skin and subcutaneous tissue disorders. Additionally, frequently reported PTs associated with alpelisib include hyperglycemia, rash, nausea, fatigue, decreased appetite, weight loss, stomatitis, and dehydration. Notably, these AEs are in accordance with information provided in the FDA's drug label and previous research on alpelisib.

For instance, a randomized phase III clinical study combining PI3K inhibitor alpelisib with fulvestrant identified hyperglycemia, rash, and diarrhea as the most common grade 3/4 AEs [9]. Similarly, a post-marketing study based on the World Health Organization pharmacovigilance database highlighted hyperglycemia, rash, diarrhea, increased blood glucose, and nausea as the most frequently reported AEs [16]. Moreover, an analysis of alpelisib's safety profile in breast cancer patients identified rash as a predominant AE, primarily affecting the trunk (78%) and extremities (70%), typically emerging within two weeks of treatment initiation [17]. This alignment of our study and previous research reinforces the significance of these findings and their applicability in real-world clinical scenarios.

In addition to known AEs, our study unearthed unexpected AEs that were not provided in FDA label. These include lip swelling,

**Table 4**
Top significant signals on the PT level (*: The instruction does not mention).

| SOC | PT | Case number(n) | ROR (95% two-sided CI) | PRR ($\chi^2$) | IC (IC025) | EBGM (EBGM05) |
|---|---|---|---|---|---|---|
| PIK3CA-mutated breast cancer | | | | | | |
| Investigations | Tumour marker decreased | 16 | 295.66 (173.17–504.79) | 295.29 (3941.86) | 0.13 (0.07) | 248.20 (145.38) |
| Investigations | Carbohydrate antigen 15-3 increased | 3 | 232.59 (69.11–782.85) | 232.54 (601.42) | 0.13 (0.04) | 202.34 (60.12) |
| Infections and infestations | Laryngitis viral* | 5 | 215.40 (84.51–548.99) | 215.31 (936.52) | 0.13 (0.05) | 189.18 (74.22) |
| Skin and subcutaneous tissue disorders | Nail cuticle fissure* | 3 | 160.41 (48.86–526.66) | 160.37 (430.59) | 0.14 (0.04) | 145.43 (44.30) |
| Metabolism and nutrition disorders | Calcification metastatic | 3 | 155.06 (47.32–508.16) | 155.03 (417.36) | 0.14 (0.04) | 141.02 (43.03) |
| Metabolism and nutrition disorders | Hyperglycaemia | 789 | 143.31 (132.96–154.46) | 134.40 (96182.52) | 0.14 (0.13) | 123.76 (114.82) |
| Congenital, familial and genetic disorders | PIK3CA-activated mutation | 17 | 120.50 (73.54–197.44) | 120.34 (1867.02) | 0.15 (0.09) | 111.74 (68.20) |
| Reproductive system and breast disorders | Rectocele* | 5 | 81.62 (33.20–200.66) | 81.59 (378.13) | 0.16 (0.06) | 77.56 (31.55) |
| Metabolism and nutrition disorders | Hyperglycaemic hyperosmolar nonketotic syndrome | 20 | 68.86 (43.98–107.80) | 68.75 (1278.58) | 0.17 (0.11) | 65.87 (42.08) |
| Investigations | Tumour marker abnormal | 8 | 65.32 (32.19–132.53) | 65.27 (485.86) | 0.17 (0.08) | 62.68 (30.89) |
| Investigations | Carbohydrate antigen 15-3 increased | 11 | 52.35 (28.70–95.50) | 52.31 (535.55) | 0.18 (0.10) | 50.63 (27.76) |
| Nervous system disorders | Coma hepatic* | 4 | 48.46 (17.91–131.12) | 48.45 (180.23) | 0.18 (0.07) | 47.01 (17.37) |
| Skin and subcutaneous tissue disorders | Dermal absorption impaired | 3 | 45.16 (14.33–142.37) | 45.15 (125.86) | 0.18 (0.06) | 43.90 (13.93) |
| Metabolism and nutrition disorders | Polydipsia | 24 | 40.00 (26.66–60.00) | 39.92 (887.88) | 0.19 (0.13) | 38.94 (25.96) |
| Respiratory, thoracic and mediastinal disorders | Nasal mucosal disorder | 3 | 34.46 (10.97–108.20) | 34.45 (95.32) | 0.20 (0.06) | 33.72 (10.74) |
| Reproductive system and breast disorders | Atrophic vulvovaginitis | 3 | 31.22 (9.95–97.92) | 31.21 (86.01) | 0.20 (0.06) | 30.62 (9.76) |
| Metabolism and nutrition disorders | Hypermetabolism* | 3 | 30.01 (9.57–94.09) | 30.01 (82.52) | 0.20 (0.07) | 29.45 (9.40) |
| Investigations | Tumour marker increased | 35 | 27.56 (19.72–38.52) | 27.49 (877.84) | 0.21 (0.15) | 27.03 (19.34) |
| Infections and infestations | Cervix disorder* | 3 | 25.99 (8.30–81.35) | 25.98 (70.87) | 0.21 (0.07) | 25.57 (8.17) |
| Gastrointestinal disorders | Bacteriuria* | 3 | 25.28 (8.08–79.12) | 25.28 (68.83) | 0.22 (0.07) | 24.89 (7.95) |
| Musculoskeletal and connective tissue disorders | Gingival erythema | 3 | 23.98 (7.67–75.01) | 23.97 (65.04) | 0.22 (0.07) | 23.62 (7.55) |
| Investigations | Bone lesion* | 15 | 23.03 (13.83–38.35) | 23.00 (311.07) | 0.22 (0.13) | 22.68 (13.62) |
| Nervous system disorders | Nutritional condition abnormal | 3 | 22.15 (7.09–69.25) | 22.15 (59.72) | 0.22 (0.07) | 21.85 (6.99) |
| Blood and lymphatic system disorders | Diabetic coma | 5 | 20.57 (8.51–49.71) | 20.56 (91.83) | 0.23 (0.10) | 20.30 (8.40) |
| Skin and subcutaneous tissue disorders | Hilar lymphadenopathy | 3 | 18.17 (5.82–56.72) | 18.17 (48.10) | 0.24 (0.08) | 17.97 (5.76) |
| Hepatobiliary disorders | Carcinoembryonic antigen increased | 7 | 17.92 (8.50–37.75) | 17.91 (110.47) | 0.24 (0.11) | 17.71 (8.41) |
| General disorders and administration site conditions | Skin toxicity | 19 | 16.81 (10.69–26.42) | 16.78 (279.02) | 0.25 (0.16) | 16.61 (10.57) |
| Respiratory, thoracic and mediastinal disorders | Hepatic mass | 7 | 16.30 (7.74–34.34) | 16.29 (99.45) | 0.25 (0.12) | 16.13 (7.66) |
| Infections and infestations | Mucosal dryness | 6 | 16.21 (7.25–36.24) | 16.20 (84.72) | 0.25 (0.11) | 16.05 (7.18) |
| | Allergic sinusitis* | 3 | 16.15 (5.18–50.38) | 16.15 (42.19) | 0.25 (0.08) | 15.99 (5.13) |
| | Colonic abscess | 3 | 15.66 (5.02–48.85) | 15.66 (40.76) | 0.25 (0.08) | 15.51 (4.97) |
| Investigations | Eosinophil count abnormal | 4 | 15.24 (5.69–40.81) | 15.24 (52.69) | 0.26 (0.10) | 15.10 (5.64) |
| Metabolism and nutrition disorders | Diabetic ketoacidosis | 67 | 15.03 (11.81–19.13) | 14.95 (864.35) | 0.26 (0.20) | 14.82 (11.64) |
| Metabolism and nutrition | | | | | | |

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**Table 4** (*continued*)

| SOC | PT | Case number(n) | ROR (95% two-sided CI) | PRR ($\chi^2$) | IC (IC025) | EBGM (EBGM05) |
|---|---|---|---|---|---|---|
| disorders Investigations | Ketoacidosis | 19 | 14.70 (9.36–23.11) | 14.68 (240.03) | 0.26 (0.16) | 14.56 (9.26) |
| Gastrointestinal disorders Hepatobiliary disorders | Blood glucose increased | 406 | 14.06 (12.73–15.53) | 13.64 (4724.82) | 0.27 (0.24) | 13.53 (12.25) |
| | Oral pain | 58 | 13.69 (10.56–17.74) | 13.63 (673.09) | 0.27 (0.21) | 13.52 (10.43) |
| | Hepatic lesion | 12 | 13.43 (7.61–23.72) | 13.42 (136.79) | 0.27 (0.15) | 13.32 (7.54) |
| Investigations Gastrointestinal disorders | Urine output increased | 5 | 12.84 (5.32–30.96) | 12.83 (54.11) | 0.27 (0.11) | 12.74 (5.28) |
| | Reflux gastritis* | 3 | 12.02 (3.86–37.44) | 12.02 (30.07) | 0.28 (0.09) | 11.93 (3.83) |
| Investigations Investigations | Blood glucose abnormal | 42 | 11.60 (8.56–15.73) | 11.57 (402.56) | 0.28 (0.21) | 11.49 (8.48) |
| Gastrointestinal disorders Gastrointestinal disorders | Blood chloride decreased* | 3 | 11.40 (3.66–35.50) | 11.40 (28.25) | 0.29 (0.09) | 11.32 (3.64) |
| Metabolism and nutrition disorders | Intra-abdominal fluid collection* | 6 | 11.20 (5.02–25.00) | 11.19 (55.30) | 0.29 (0.13) | 11.12 (4.98) |
| | Dysbiosis* | 3 | 11.16 (3.58–34.73) | 11.15 (27.53) | 0.29 (0.09) | 11.08 (3.56) |
| | Food aversion | 3 | 11.05 (3.55–34.40) | 11.05 (27.22) | 0.29 (0.09) | 10.98 (3.53) |
| Reproductive system and breast disorders | Vulvovaginal dryness | 6 | 10.90 (4.88–24.33) | 10.89 (53.53) | 0.29 (0.13) | 10.82 (4.85) |
| Psychiatric disorders Respiratory, thoracic and mediastinal disorders | Impatience* | 3 | 10.84 (3.48–33.76) | 10.84 (26.61) | 0.29 (0.09) | 10.77 (3.46) |
| | Pharyngeal ulceration | 3 | 10.55 (3.39–32.84) | 10.55 (25.75) | 0.30 (0.09) | 10.48 (3.37) |
| Gastrointestinal disorders Infections and infestations | Stomatitis | 131 | 10.46 (8.80–12.43) | 10.36 (1101.61) | 0.30 (0.25) | 10.30 (8.66) |
| Reproductive system and breast disorders | Lung abscess | 4 | 10.36 (3.87–27.69) | 10.35 (33.57) | 0.30 (0.11) | 10.29 (3.85) |
| Musculoskeletal and connective tissue disorders Renal and urinary disorders | Breast disorder | 4 | 10.29 (3.85–27.50) | 10.28 (33.30) | 0.30 (0.11) | 10.22 (3.82) |
| General disorders and administration site conditions | Spinal deformity* | 3 | 10.20 (3.28–31.75) | 10.20 (24.73) | 0.30 (0.10) | 10.14 (3.26) |
| Gastrointestinal disorders General disorders and administration site conditions Gastrointestinal disorders | Polyuria* | 16 | 10.16 (6.21–16.61) | 10.14 (131.05) | 0.30 (0.18) | 10.09 (6.17) |
| | Thirst | 36 | 9.93 (7.15–13.79) | 9.90 (286.44) | 0.30 (0.22) | 9.85 (7.09) |
| Gastrointestinal disorders Psychiatric disorders | Oral mucosal eruption | 3 | 9.75 (3.13–30.35) | 9.75 (23.41) | 0.31 (0.10) | 9.70 (3.12) |
| Metabolism and nutrition disorders | Mucosal inflammation | 46 | 9.52 (7.12–12.73) | 9.49 (347.48) | 0.31 (0.23) | 9.44 (7.06) |
| Investigations Metabolism and nutrition disorders | Gingival pain | 12 | 9.51 (5.39–16.78) | 9.50 (90.73) | 0.31 (0.17) | 9.45 (5.36) |
| | Lip disorder | 3 | 9.44 (3.03–29.36) | 9.43 (22.48) | 0.31 (0.10) | 9.38 (3.02) |
| | Eating disorder* | 39 | 9.24 (6.74–12.67) | 9.22 (284.08) | 0.31 (0.23) | 9.17 (6.69) |
| | Feeding disorder* | 42 | 9.17 (6.77–12.43) | 9.15 (303.10) | 0.31 (0.23) | 9.10 (6.72) |
| | Blood glucose fluctuation | 14 | 8.80 (5.20–14.88) | 8.79 (96.13) | 0.32 (0.19) | 8.75 (5.17) |
| | Diabetic metabolic decompensation | 4 | 8.79 (3.29–23.48) | 8.78 (27.43) | 0.32 (0.12) | 8.74 (3.27) |
| Gastrointestinal disorders Gastrointestinal disorders | Diverticulum intestinal* | 5 | 8.77 (3.64–21.13) | 8.77 (34.22) | 0.32 (0.13) | 8.72 (3.62) |
| Congenital, familial and genetic disorders | Gastric polyps* | 3 | 8.73 (2.81–27.15) | 8.73 (20.41) | 0.32 (0.10) | 8.68 (2.79) |
| Nervous system disorders Gastrointestinal disorders | Gene mutation | 5 | 8.52 (3.54–20.52) | 8.52 (33.00) | 0.32 (0.13) | 8.48 (3.52) |
| Infections and infestations Gastrointestinal disorders | Taste disorder* | 63 | 8.40 (6.56–10.77) | 8.37 (406.74) | 0.33 (0.26) | 8.33 (6.50) |
| General disorders and administration site conditions | Cheilitis | 6 | 8.36 (3.75–18.65) | 8.36 (38.66) | 0.33 (0.15) | 8.32 (3.73) |
| Gastrointestinal disorders Metabolism and nutrition | Dysentery* | 3 | 7.97 (2.56–24.77) | 7.96 (18.17) | 0.33 (0.11) | 7.93 (2.55) |

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**Table 4** (*continued*)

| SOC | PT | Case number(n) | ROR (95% two-sided CI) | PRR ($\chi^2$) | IC (IC025) | EBGM (EBGM05) |
|---|---|---|---|---|---|---|
| disorders Psychiatric disorders | Oral disorder | 10 | 7.75 (4.16–14.43) | 7.74 (58.44) | 0.34 (0.18) | 7.71 (4.14) |
| Metabolism and nutrition disorders | Mucosal disorder | 3 | 7.56 (2.43–23.52) | 7.56 (17.00) | 0.34 (0.11) | 7.53 (2.42) |
| Gastrointestinal disorders Gastrointestinal disorders | Oral mucosal blistering | 9 | 7.33 (3.81–14.12) | 7.33 (48.95) | 0.35 (0.18) | 7.30 (3.79) |
| Skin and subcutaneous tissue disorders | Diabetes mellitus | 96 | 7.33 (5.99–8.96) | 7.28 (518.25) | 0.35 (0.29) | 7.25 (5.93) |
| | Negative thoughts | 3 | 7.03 (2.26–21.85) | 7.03 (15.43) | 0.36 (0.11) | 7.00 (2.25) |
| | Insulin resistance | 3 | 6.87 (2.21–21.36) | 6.87 (14.98) | 0.36 (0.12) | 6.84 (2.20) |
| | Oral pruritus | 3 | 6.83 (2.20–21.24) | 6.83 (14.86) | 0.36 (0.12) | 6.80 (2.19) |
| | Tongue discomfort* | 8 | 6.72 (3.36–13.46) | 6.72 (38.77) | 0.36 (0.18) | 6.69 (3.34) |
| | Rash | 589 | 6.66 (6.13–7.24) | 6.40 (2691.46) | 0.37 (0.34) | 6.38 (5.87) |
| Gastrointestinal disorders Gastrointestinal disorders | Mouth swelling | 9 | 6.52 (3.39–12.55) | 6.52 (41.86) | 0.37 (0.19) | 6.49 (3.37) |
| Gastrointestinal disorders Gastrointestinal disorders | Tongue discolouration* | 4 | 6.28 (2.35–16.78) | 6.28 (17.70) | 0.38 (0.14) | 6.26 (2.34) |
| | Aphthous ulcer | 14 | 6.25 (3.69–10.56) | 6.24 (61.37) | 0.38 (0.22) | 6.22 (3.68) |
| | Dry mouth | 79 | 5.96 (4.77–7.43) | 5.92 (322.50) | 0.39 (0.31) | 5.91 (4.73) |
| Vascular disorders Nervous system disorders | Hypovolaemic shock | 5 | 5.69 (2.36–13.69) | 5.69 (19.24) | 0.40 (0.17) | 5.67 (2.36) |
| Skin and subcutaneous tissue disorders | Central nervous system lesion | 13 | 5.68 (3.29–9.79) | 5.67 (49.88) | 0.40 (0.23) | 5.66 (3.28) |
| Nervous system disorders Gastrointestinal disorders | Skin reaction | 15 | 5.52 (3.32–9.16) | 5.51 (55.23) | 0.41 (0.24) | 5.50 (3.31) |
| Metabolism and nutrition disorders | Parosmia* | 7 | 5.23 (2.49–11.00) | 5.23 (23.89) | 0.42 (0.20) | 5.22 (2.48) |
| | Abnormal faeces | 9 | 5.08 (2.64–9.77) | 5.08 (29.36) | 0.43 (0.22) | 5.06 (2.63) |
| | Decreased appetite | 230 | 5.07 (4.45–5.78) | 5.00 (736.07) | 0.43 (0.38) | 4.99 (4.38) |
| Musculoskeletal and connective tissue disorders | Osteonecrosis of jaw* | 16 | 5.02 (3.07–8.21) | 5.02 (51.32) | 0.43 (0.26) | 5.01 (3.06) |
| Metabolism and nutrition disorders | Glucose tolerance impaired | 5 | 4.90 (2.03–11.78) | 4.89 (15.44) | 0.44 (0.18) | 4.88 (2.03) |
| Investigations | Glycosylated haemoglobin increased | 24 | 4.80 (3.22–7.17) | 4.80 (71.91) | 0.44 (0.30) | 4.78 (3.20) |
| Respiratory, thoracic and mediastinal disorders | Dry throat | 9 | 4.69 (2.44–9.03) | 4.69 (26.07) | 0.45 (0.23) | 4.68 (2.43) |
| Gastrointestinal disorders Vascular disorders | Lip swelling* | 27 | 4.68 (3.21–6.83) | 4.67 (77.79) | 0.45 (0.31) | 4.66 (3.20) |
| Gastrointestinal disorders Investigations | Lymphoedema* | 7 | 4.63 (2.20–9.72) | 4.63 (19.84) | 0.45 (0.22) | 4.61 (2.20) |
| Gastrointestinal disorders | Retching | 16 | 4.53 (2.77–7.40) | 4.53 (43.84) | 0.46 (0.28) | 4.52 (2.76) |
| | Weight decreased | 237 | 4.29 (3.77–4.87) | 4.22 (584.17) | 0.48 (0.42) | 4.22 (3.71) |
| | Diarrhea | 544 | 4.28 (3.93–4.67) | 4.14 (1306.14) | 0.49 (0.45) | 4.13 (3.79) |
| Musculoskeletal and connective tissue disorders | Muscle atrophy* | 8 | 4.06 (2.03–8.12) | 4.06 (18.37) | 0.50 (0.25) | 4.05 (2.02) |
| Gastrointestinal disorders Investigations | Colitis | 32 | 4.01 (2.84–5.68) | 4.01 (72.03) | 0.50 (0.35) | 4.00 (2.82) |
| Skin and subcutaneous tissue disorders | Blood creatinine increased | 47 | 3.98 (2.99–5.30) | 3.97 (104.24) | 0.50 (0.38) | 3.96 (2.97) |
| Metabolism and nutrition disorders | Rash maculo-papular | 17 | 3.96 (2.46–6.37) | 3.95 (37.40) | 0.51 (0.31) | 3.94 (2.45) |
| Investigations | Dehydration | 79 | 3.66 (2.93–4.56) | 3.64 (151.13) | 0.54 (0.43) | 3.63 (2.91) |
| | Liver function test increased | 20 | 3.56 (2.29–5.52) | 3.55 (36.65) | 0.55 (0.35) | 3.55 (2.29) |

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**Table 4** (*continued*)

| SOC | PT | Case number(n) | ROR (95% two-sided CI) | PRR ($\chi^2$) | IC (IC025) | EBGM (EBGM05) |
|---|---|---|---|---|---|---|
| Respiratory, thoracic and mediastinal disorders | Pleural effusion* | 35 | 3.38 (2.42–4.71) | 3.37 (58.36) | 0.57 (0.41) | 3.37 (2.42) |
| Gastrointestinal disorders | Swollen tongue* | 16 | 3.32 (2.03–5.42) | 3.31 (25.80) | 0.58 (0.35) | 3.31 (2.03) |
| Respiratory, thoracic and mediastinal disorders | Pneumonitis | 19 | 3.26 (2.08–5.11) | 3.26 (29.65) | 0.59 (0.37) | 3.25 (2.07) |
| Nervous system disorders | Dysgeusia* | 34 | 2.97 (2.12–4.16) | 2.97 (44.30) | 0.64 (0.46) | 2.96 (2.12) |
| Gastrointestinal disorders | Nausea | 360 | 2.56 (2.30–2.84) | 2.51 (331.37) | 0.75 (0.68) | 2.51 (2.26) |
| Gastrointestinal disorders | Vomiting | 205 | 2.53 (2.20–2.90) | 2.50 (185.52) | 0.76 (0.66) | 2.50 (2.18) |
| General disorders and administration site conditions | Asthenia | 161 | 2.39 (2.04–2.79) | 2.37 (127.66) | 0.81 (0.69) | 2.37 (2.02) |
| General disorders and administration site conditions | Fatigue | 361 | 2.28 (2.06–2.54) | 2.25 (253.02) | 0.86 (0.77) | 2.25 (2.02) |
| PIK3CA-related overgrowth spectrum | | | | | | |
| Congenital, familial and genetic disorders | Vascular malformation | 3 | 1365.63 (430.03–4336.77) | 1357.95 (3922.59) | 0.10 (0.03) | 1309.49 (412.35) |
| Musculoskeletal and connective tissue disorders | Scoliosis | 3 | 57.70 (18.53–179.63) | 57.38 (165.94) | 0.17 (0.05) | 57.29 (18.40) |
| Metabolism and nutrition disorders | Hyperglycaemia | 10 | 37.80 (20.21–70.69) | 37.11 (351.19) | 0.19 (0.10) | 37.07 (19.82) |
| Investigations | Glycosylated haemoglobin increased | 6 | 28.60 (12.79–63.97) | 28.29 (157.90) | 0.21 (0.09) | 28.27 (12.64) |
| General disorders and administration site conditions | Drug effect less than expected | 3 | 23.02 (7.40–71.62) | 22.89 (62.78) | 0.22 (0.07) | 22.88 (7.35) |
| Gastrointestinal disorders | Oral pain | 3 | 16.62 (5.34–51.72) | 16.54 (43.78) | 0.25 (0.08) | 16.53 (5.31) |
| Gastrointestinal disorders | Stomatitis | 8 | 15.08 (7.50–30.32) | 14.87 (103.56) | 0.26 (0.13) | 14.86 (7.39) |
| Musculoskeletal and connective tissue disorders | Limb discomfort | 4 | 12.97 (4.85–34.68) | 12.88 (43.83) | 0.27 (0.10) | 12.87 (4.81) |
| Infections and infestations | Cellulitis* | 5 | 12.61 (5.23–30.42) | 12.50 (52.92) | 0.27 (0.11) | 12.50 (5.18) |
| Skin and subcutaneous tissue disorders | Alopecia | 13 | 7.05 (4.07–12.22) | 6.90 (65.83) | 0.36 (0.21) | 6.90 (3.98) |
| Psychiatric disorders | Suicide attempt* | 3 | 6.99 (2.25–21.75) | 6.96 (15.32) | 0.36 (0.11) | 6.96 (2.24) |
| General disorders and administration site conditions | Swelling | 5 | 5.65 (2.34–13.62) | 5.60 (18.93) | 0.40 (0.17) | 5.60 (2.32) |
| Investigations | Blood glucose increased | 7 | 5.57 (2.64–11.75) | 5.51 (25.92) | 0.41 (0.19) | 5.51 (2.62) |
| Investigations | Weight decreased | 10 | 4.27 (2.28–7.97) | 4.20 (24.53) | 0.48 (0.26) | 4.20 (2.25) |
| Metabolism and nutrition disorders | Decreased appetite | 8 | 4.15 (2.06–8.34) | 4.10 (18.81) | 0.49 (0.24) | 4.10 (2.04) |
| Gastrointestinal disorders | Diarrhea | 22 | 4.08 (2.66–6.25) | 3.95 (48.98) | 0.50 (0.33) | 3.95 (2.58) |
| General disorders and administration site conditions | Pyrexia | 11 | 4.00 (2.20–7.26) | 3.93 (24.19) | 0.51 (0.28) | 3.93 (2.16) |

SOC, system organ class; PT, preferred term; ROR, reporting odds ratio; CI, confidence interval; PRR, proportional reporting ratio; χ2, chi-information component; IC, information component; IC025, the lower limit of 95% CI of the IC; EBGM, empirical Bayesian geometric mean; EBGM05, the lower limit of 95% CI of EBGM.

reflux gastritis, diverticulum intestinal, intra-abdominal fluid collection, tongue discomfort, bacteriuria, laryngitis viral, vulvovaginal candidiasis, decreased blood chloride, hepatic coma, feeding disorder, eating disorder, parosmia, cervix disorder, rectocele, allergic sinusitis, polyuria, pleural effusion, nail cuticle fissure, onychoclasis, and lymphoedema. Previous post-marketing drug safety study for alpelisib, utilizing the World Health Organization (WHO) pharmacovigilance database, revealed several unexpected AEs similar to our study. These included lip swelling (ROR = 2.78, IC025 = 0.60), intra-abdominal fluid collection (ROR = 30.22, IC025 = 1.09), feeding disorder (ROR = 17.03, IC025 = 3.03), eating disorder (ROR = 15.11, IC025 = 2.81), polyuria (ROR = 9.50, IC025 = 1.72), pleural effusion (ROR = 7.20, IC025 = 1.90), and lymphoedema (ROR = 11.74, IC025 = 1.30) [16]. Among these, polyuria may be associated with hyperglycemia, a known AE documented by the FDA. Additionally, polyuria may also be linked to diabetes insipidus or poor renal function. Besides AEs excavated from WHO pharmacovigilance database, other AEs in our study represent unexpected findings not previously mentioned in the literature. As such, these AEs merit further validation to enhance the clinical medication safety of

alpelisib. However, there are not mechanism studies associated with these unexpected AEs and further exploration is needed.

Occurrences such as PIK3CA-activated mutation, death, disease progression, hilar lymphadenopathy, lymphatic malformation, vascular malformation, gene mutation, product distribution issue, product supply issue, and breast disorder were not initially classified as alpelisib-induced AEs. These events are more likely intertwined with the natural progression of the primary disease and supply-related issues. Notably, hilar lymphadenopathy is a frequent pattern of cancer spread, especially in primary lung malignancies [18]. Furthermore, lymphatic and vascular malformations are common clinical manifestations of PROS conditions [6]. Recognizing these distinctions is crucial for a comprehensive understanding of the patient's condition and effective treatment management.

Previous studies have established that the occurrence of adverse drug reactions is significantly influenced by gender, age, and concomitant drugs [19–21]. Therefore, we stratified patients by gender, age, and concomitant use or non-use to investigate whether newly detected disproportionate AEs in the entire study population remained disproportionate after stratification. We observed that the unexpected disproportionate AEs identified in the overall study populations continued to be disproportionate in groups of females, adults, those with concomitant drug use, and those without concomitant drug use.

PIK3CA-mutated breast cancer patients constituted the vast majority of the population we collected from the FAERS database, and breast cancer occurs more commonly in adult women [22]. Therefore, these unexpected AEs were not detected in males and juveniles, possibly due to their small sample size. We believe that further research for stratified populations is necessary due to the absence of AE incidence in the FAERS database. We found the time-to-onset of different unexpected AEs was not consistent. Due to limitation of FAERS database, we got only a small quantity of time-to-onset data. It is expected that more studies will conduct in-depth research on this aspect in the future.

Given the distinct indications for alpelisib, we stratified the populations into two groups based on their indications for further research. Comparation of the general clinical characteristics between two groups revealed significant differences in gender, age, weight, and the reporting rate of serious outcomes. Even though we can not get the accurate difference of clinical characteristics between patients with distinct indication because of the limitation of FAERS database. It is still worth noting that the occurrence of alpelisib-associated AEs may vary between patients with PIK3CA-mutated breast cancer and those with PROS, which need further study. The number of reported serious outcomes caused by AEs is notably different between patients with these distinct diseases. For example, the toll of reported adverse reactions resulting in death is higher in PIK3CA-mutated breast cancer patients compared to PROS patients. However, due to the inherent limitations of a SRS, this does not indicate that the mortality associated alpelisib is different between distinct indications. Besides, lethality is influenced by many confounding factors, such as the higher mortality rate associated with malignant tumors, different time to market as well as varied dosages, necessitating further investigation.

In our exploration of AEs associated with alpelisib specifically in PROS patients, we uncovered unexpected findings, notably suicide attempts and cellulitis. These were considered significant AEs when alpelisib was used for PROS, but were not detected in the treatment of PIK3CA-mutated breast cancer patients, according to our study and the FDA's drug label. Therefore, whether suicide attempts or cellulitis are AEs associated with alpelisib used for PIK3CA-mutated breast cancer requires further investigation through randomized clinical studies. Furthermore, compared to PROS patients, those with breast cancer taking alpelisib experienced a greater variety of AEs. This phenomenon may be attributed to the larger sample size, and further controlled experiments are needed for verification. In our additional analysis of PROS patients, we discovered suicide as a novel AE not previously mentioned in safety research on alpelisib. Suicide has been identified as an adverse reaction to multiple drugs, potentially resulting in serious consequences [23–25]. However, it cannot be ruled out that suicide attempts may arise from the progression of the disease state or anxiety about treatment and be influenced by concomitant medications. To sum up, suicide, as a serious outcome, is worthy of attention when using alpelisib for PROS and warrants further investigation. Similarly, when we analyzed PIK3CA-mutated breast cancer patients treated with alpelisib, we identified additional novel AEs. Therefore, it is meaningful to categorize patients into different study populations according to their indication for the analysis of AEs associated with alpelisib.

### *4.1. Limitations of the study*

While the benefits of conducting large-scale population studies in the real world using the FAERS database are undeniable, there were several limitations inherently associated with all pharmacovigilance databases. A number of factors need to be taken into consideration to ensure a balanced interpretation of our study's results. Firstly, the voluntary nature of the FAERS database, which underpins our study, introduces the potential for arbitrary reporting, biases, and underreporting. This variability in data quality could inevitably influence the accuracy and comprehensiveness of the results. Secondly, the absence of critical clinical details and information about the multiple drugs used in combination with alpelisib poses a challenge in controlling for confounding variables, potentially impacting the reliability of the conclusions [26]. Furthermore, due to the absence of accurate patient numbers using alpelisib, it remains impossible to calculate the true incidence rates for each identified AE.

It is crucial to acknowledge that although data mining techniques cannot compensate for the inherent limitations of a SRS, the combined utilization of the large-scale database and case reports remains an effective approach for delving into adverse drug reactions [27]. The insights gleaned from this methodology provide valuable preliminary information, offering avenues for further investigation and prospective studies. Although the findings should be interpreted with caution, they represent contributions to a broader understanding of the safety profile of alpelisib and its potential implications in clinical practice.

## 5. Conclusion

Through a comprehensive and systematic analysis of the FAERS database, we embarked on an assessment of the post-marketing

safety profile linked to alpelisib. The AE signals we identified closely align with the information provided in the FDA's official prescribing guidelines. Notably, our study unveiled twenty-one unexpected and significant AEs, expanding upon the existing knowledge derived from pre-marketing clinical trials. When we conducted separate analyses for patients with distinct indications, we made noteworthy discoveries associated with alpelisib's safety profile. These findings are particularly valuable in addressing the limitations of pre-marketing trials and serve as a crucial resource for ensuring drug safety. To establish a definitive connection between alpelisib and these newly identified AEs, further prospective clinical trials are imperative. Our study introduces a fresh perspective to the realm of clinical safety assessments concerning alpelisib, ultimately advancing our understanding in this field.

## Ethics approval and consent to participate

Our study is a secondary analysis of publicly available summary statistics and requires no specific ethical approval.

## Data availability statement

All data generated or analyzed during this article are included in the published article (and in its supplementary information files).

## CRediT authorship contribution statement

**Yu Lin:** Writing – review & editing, Data curation, Conceptualization. **Xinlei Zheng:** Writing – original draft, Investigation, Formal analysis, Data curation. **Yan Chen:** Writing – review & editing, Writing – original draft. **Qichun Nian:** Writing – review & editing, Data curation. **Li Lin:** Writing – review & editing, Writing – original draft, Data curation. **Maohua Chen:** Writing – review & editing, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e27529.

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