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Research article

Alpelisib-related adverse events: The FDA Adverse Event Reporting System Database (FAERS) pharmacovigilance study

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ABSTRACT

Background: Alpelisib was approved for treatment of breast cancer. We assessed the safety signals associated with alpelisib by data mining the FDA pharmacovigilance database.
Methods: Data from the second quarter of 2019 to the fourth quarter of 2022 had been retrieved from the FAERS database. Disproportionality analysis by reporting odds ratio were used to evaluate the potential association between adverse events (AEs) and alpelisib.
Results: A total of 5,980,090 reports were extracted, 18,149 of them were chosen with alpelisib as the suspected drug. After combining the same PRIMARYID, 5647 patients remained. We observed 10 system organ classes (SOCs) with a reported number >50 and associated with alpelisib as gastrointestinal disorders, general disorders and administration site conditions, metabolism and nutrition disorders, skin and subcutaneous tissue disorders, investigations and neoplasms benign, malignant and unspecified (incl cysts and polyps), immune system disorders, nervous system disorders, psychiatric disorders, eye disorders. The median time to AEs in these patients was 13 days, with an IQR (Interquartile Range) of 7–70 days. 61.12% AEs happened within the initial month of alpelisib usage.
Conclusion: Our study provided a more in-depth and extensive understanding of AEs that may be associated with alpelisib, which will help to reduce the risk of AEs in the clinical treatment of alpelisib. AEs with novel preferred term (PTs) were constipation, dysphagia, diabetic ketoacidosis, feeding disorder, urticaria, eye disorders and vision blurred. 61.12% of cases developed AEs within 30 days after taking alpelisib.

1. Introduction

Breast cancer is the most common cancer among women and one of the deadly cancers in women worldwide [1,2]. PI3Ks are a family of lipid kinases that have four catalytic isoforms: α, β, γ and δ [3,4]. Class I PI3Ks are subdivided into subclass IA and subclass IB, where class IA PI3Ks are heterodimers consisting of a p110α catalytic subunit and a p85 regulatory subunit [5]. Notably, PIK3CA is an oncogene encoding the catalytic isoform of p110α [6]. $HER2^+$ and HR^+ breast cancers are the two most common subtypes in which this

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mutation occurs [7].

Alpelisib is an oral α-specific PI3K inhibitor (PI3Ki) that selectively inhibits PI3Kα isoforms and is 50 times more potent against PI3Kα than other class I isoforms β, δ and γ [8]. The FDA approved alpelisib in May 2019 for the treatment of postmenopausal HR^+/$HER2^-$, PIK3CA-mutated advanced or metastatic breast cancer progressing or following an endocrine regimen [9]. Preclinical and clinical studies had reported remarkable effectiveness of alpelisib in tumors with GOF PIK3CA mutations [10–13]. In addition, Studies had shown that targeting PI3Kα had more potential to reduce treatment-related toxicity and improve the therapeutic window than other less specific isoform inhibitors. Alpelisib had shown single-agent activity in patients with advanced solid tumors with PIK3CA mutations [14]. Successful clinical treatment of solid tumors using alpelisib to target the PI3K pathway [15]. Alpelisib improved progression-free survival (PFS) in patients with PIK3CA mutations by tumor sequencing or circulating tumor DNA [16].

After its approval, alpelisib has raised postmarketing concerns for its long-term safety and clinical tolerability. A thorough comprehension of the safety of alpelisib will facilitate the appropriate detection and management of AEs. Currently, the most common grade 3 or 4 AEs reported with alpelisib were hyperglycemia and macular papules [17]. It had also been shown that the AEs profile of alpelisib plus fulvestrant in SOLAR-1 showed hyperglycemia, diarrhea and rash in the most frequent grade 3/4 AEs [12]. Hematologic toxicity and peripheral neuropathy were also reported in a phase I/II study of alpelisib + nab-paclitaxel for HER2-metastatic breast cancer [18]. Besides, in this study alpelisib was discontinued in 25% of patients due to AEs such as hyperglycemia, rash and diarrhea and 12 patients discontinued treatment due to toxicity (2 cases of pneumonia; 1 case each of infection, thrombocytopenia, and renal dysfunction). With the extensive utilization of alpelisib, a systematic and comprehensive presentation of alpelisib-induced changes in AEs would be beneficial to clinicians and pharmacovigilance specialists. Thus, AEs associated with alpelisib were the focus of this study.

Therefore, this study interrogated the FDA Adverse Event Reporting System (FAERS) to analyze the safety data of alpelisib based on the FAERS database, which is a global and publicly accessible pharmacovigilance database [19]. Further, we performed descriptive analyses, disproportionality analysis, and time to onset to detect characteristics of alpelisib -associated AEs.

This study provided updated findings on the safety profile of postmarketing alpelisib-related AEs in a real population based on the FAERS database. Our results were consistent with previous clinical trials and literature reviews that alpelisib was associated with AEs such as diarrhea, hyperglycemia, and rash. Besides our report analyzed other AEs as well, and our report also presented a more accurate and detailed description and characterization of alpelisib-associated AEs, with the innovative addition of categorical analysis,

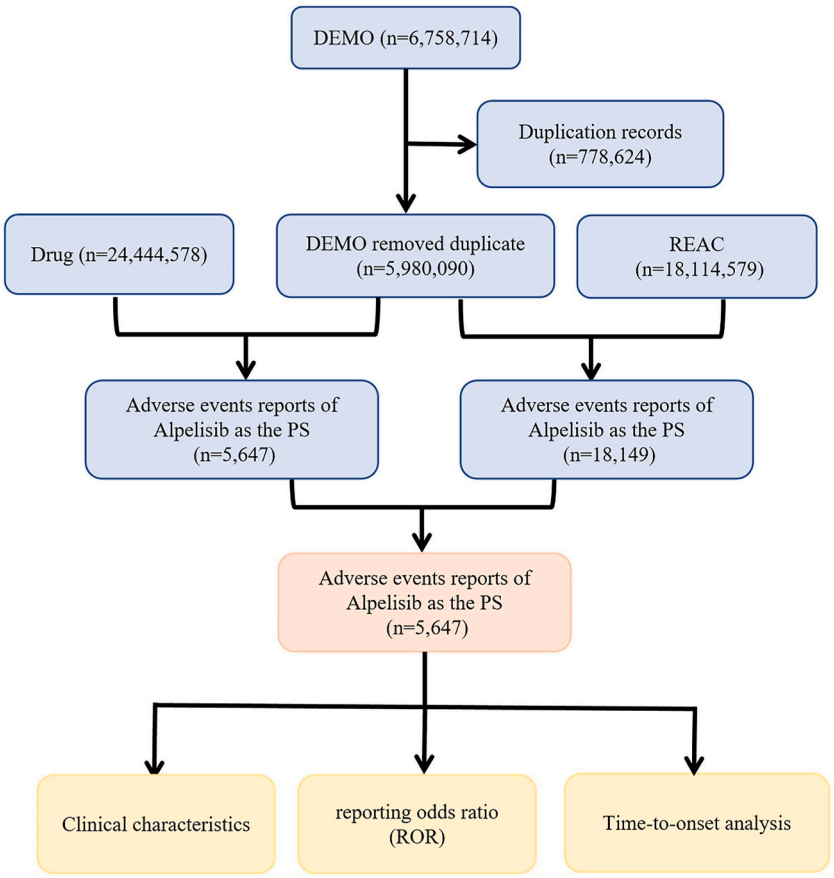

Fig. 1. The process of selecting alpelisib -associated adverse events from food and drug administration adverse event reporting database.

disproportionality analysis, and number of reported cases.

2. Results

2.1. Descriptive analysis

During the study period, a total of 5,980,090 AE reports were obtained from the FAERS database after exclusion of duplicates, containing 18,149 alpelisib-related AEs in 5647 patients (Fig. 1). The detailed clinical characteristics were summarized in Table 1. Of the patients whose gender was reported, 4932 were female (87.34%) and 198 were male (3.51%). Age data were available for 1883 patients, there were 1853 patients over the age of 18. Of the 773 patients who reported weight data for alpelisib treatment, 617 in patients with lower body weight (<80 kg) and 156 in patients with higher body weight (>80 kg). Serious outcomes of overall AEs reports were recorded in 3440 cases, of which 23.72% (n = 816) died, 29.91% (n = 1029) were hospitalized, and 41.54% (n = 1429) had other serious adverse events (Table 2). In addition, the alpelisib-related AEs reported by healthcare professionals and by consumers was 2640 (46.75%) and 2645 (47.00%), respectively.

2.2. Disproportionality analysis

Compared with non-alpelisib-related AEs, alpelisib-related AEs showed an imbalance in 42 AEs were reported in FAERS database in at least 50 cases and the lower limit of 95% confidence interval >1. Results of the disproportionality analysis of the AEs associated with alpelisib were presented in Fig. 2. The results included 10 SOCs: gastrointestinal disorders, general disorders and administration site conditions, metabolism and nutrition disorders, skin and subcutaneous tissue disorders, investigations and neoplasms benign, malignant and unspecified (incl cysts and polyps), immune system disorders, nervous system disorders, psychiatric disorders, eye disorders. 10 PTs associated with gastrointestinal disorders (n = 2652). 10 PTs associated with general disorders and administration site conditions (n = 2221). 6 PTs associated with metabolism and nutrition disorders (n = 1830). 5 PTs associated with metabolism and nutrition disorders (n = 1470). 4 PTs associated with investigations (n = 1314). 3 PTs associated with neoplasms benign, malignant and unspecified (incl cysts and polyps) (n = 366). 1 PT associated with immune system disorders (n = 100). 1 PT associated with nervous system disorders (n = 87). 1 PT associated with psychiatric disorders (n = 63). 1 PT associated with eye disorders (n = 50).

Table 1
Clinical characteristics of patients with alpelisib-associated adverse events.

Clinical characteristics	Total reports	Percentage
Gender		
Female	4932	87.34%
Male	198	3.51%
Unkown or missing	517	9.16%
Age (years)		
<18	30	0.53%
18–64	920	16.29%
≥65	933	16.52%
Unkown or missing	3764	66.65%
Weight		
<80	617	10.93%
80–100	114	2.02%
>100	42	0.74%
NA	4874	86.31%
Reported countries		
US	3676	65.10%
Non-US	1971	34.90%
Reporters		
Consumer	2654	47.00%
Health professional	765	13.55%
Physician	1414	25.04%
Other health-professional	174	3.08%
Pharmacist	287	5.08%
NA	353	6.25%
Reporting year		
22	1544	27.34%
21	1651	29.24%
20	1728	30.60%
19	724	12.82%
Outcome of adverse events		
Serious outcome	3440	60.92%
Missing/Non-serious outcome	2207	39.08%

NA: not reported.

Table 2
Serious outcomes of overall adverse events reports.

Serious outcome of adverse events	Total reports	Percentage
Hospitalization	1029	29.91%
Death	816	23.72%
Life-threatening	110	3.20%
Disability	38	1.10%
Required intervention to prevent permanent impairment	18	0.52%
Other serious outcome	1429	41.54%

NA: not reported.

2.3. Time to onset of alpelisib-associated AEs

Of the 5647 patients, only 1124 (19.90%) were available for time analysis. The median time to AEs in these patients was 13 days, with an IQR of 7–70 days. In Fig. 3, it can be seen that most AEs in these patients (61.12%) happened within the initial month of alpelisib usage. We also analyzed onset time of five SOCs individually in Fig. 3. Gastrointestinal disorders had a median onset time of 10 days, with an IQR of 2–34.5 days and 72.14% of cases developed within 30 days after taking alpelisib. General disorders and administration site conditions had a median onset time of 12 days, with an IQR of 6–51 days, and 63.99% of cases developed within 30 days after taking alpelisib. Metabolism and nutrition disorders had a median onset time of 11 days, with an IQR of 3–27.5 days. 73.68% of cases developed within 30 days after taking alpelisib. The median time to skin and subcutaneous tissue disorders was 10 days, with an IQR of 5–16 days. 80.87% of cases developed within 30 days after taking alpelisib. The median time to neoplasms benign, malignant and unspecified (incl cysts and polyps) was 15 days, with an IQR of 4–57.5 days and 63.20% of cases developed within 30 days after taking alpelisib.

3. Discussion

An increasing number of studies have begun to focus on alpelisib, and it has been suggested that alpelisib can extend the life span of organisms by an average of 10%, up to 3 years [20]. Therefore, it is essential to understand the AEs of alpelisib. With the widespread availability of alpelisib, various AEs, especially for new documented signals, should be labeled as safety warnings by clinicians. This study presented updated findings on the safety profile of post-marketing alpelisib-related AEs in a real-world population based on the FAERS database. To our understanding, we were the first to conduct the most comprehensive study of alpelisib AEs through the FAERS database. In 2021, Chen et al. studied the AEs of alpelisib based on this database of VigiBase database. In our study, a total of 5, 647 patients of AEs of alpelisib were retained from 2019 to 2022, while CHEN et al. reported only 687 cases from 2019 to 2021 [21]. Notably our report presented a more accurate and detailed description of alpelisib AEs, with the disproportionality analysis and an assessment of time to onset of AEs.

In order to better understand the AEs of alpelisib, our study was screened to report the number of AEs occurring in at least 50 cases and the lower limit of 95% confidence interval >1. According to disproportionality analysis, the most common signals at the SOC level were gastrointestinal disorders, general disorders and administration site conditions, metabolism and nutrition disorders, skin and subcutaneous tissue disorders, investigations and neoplasms benign, malignant and unspecified (incl cysts and polyps). The occurrence of the above SOCs was also confirmed in CHEN et al. [21]. This is consistent with our results.

Among the gastrointestinal disorders, the most common PTs were diarrhaea, nausea and vomiting. A phase 1b trial confirmed the occurrence of PTs as described above, consistent with our results [22]. Interestingly, we also identified two new PTs that may be related to alpelisib, which have not been reported in the FDA specification and other literature; they are constipation, dysphagia. The top three reported cases in general disorders and administratian site conditions were death, fatigue and asthenia. In metabolism and nutriton disorders, the top three PTs reported cases are hyperglycaemia, decreased appetite and dehydration. These PTs were also reported by other studies [23,24]. Diabetic ketoacidosis and feeding disorder were not reported in the FDA specification or other literature. The most common PTs reported cases in skin and subcutaneous tissue disorders were rash, pruritus and alopecia, while we identified urticaria as a novel AE associated with alpelisib. Our results are consistent with other studies [25–27]. A total of three PTs were reported in neoplasms benign, malignant and unspecified (incl cysts and polyps): mallignant neoplasm progression, breast cancer metastatic and metastases to liver. These PTs for metastatic malignant tumors were of concern in clinical dosing to avoid disease progression. We also found that alpelisib was also associated with hypersensitivity. In a previous basic study it was shown that deletion of NEDD9 or BCL-XL resulted in sensitization of gastric cancer cells to alpelisib [28]. Finally, we identified novel PTs not documented in the FDA specification for alpelisib as eye disorders and vision blurred.

We reported for the first time the median onset time of alpelisib -related AEs. This research suggested that the median onset time of erdafitinib-induced AEs following initial treatment was 13 days, with an IQR of 7–70 days. A significant proportion of AEs were in the first month after the start of alpelisib treatment (n = 687, 61.12%). Comparison of the SOCs that were analyzed separately for the timing of adverse reactions revealed that adverse reactions in these SOCs were also clustered at one month after starting alpelisib. Therefore, healthcare professionals should focus on monitoring during this period so that AEs do not affect the effectiveness of treatment or the course of the disease. However, it should be noted that our study included only 1124 AE reports with documented time of onset, which may limit the accurate reflection of actual time of onset and requires further validation. Therefore, it is important for

adverse.event	Alpelisib.n (N=18149)	Non.Alpelisib.n (N=18096430)	ROR	95%CI
Gastrointestinal disorders				
Diarrhoea	935	187413	5.19	[4.86,5.54]
Nausea	577	204258	2.88	[2.65,3.13]
Vomiting	330	116609	2.86	[2.56,3.18]
Stomatitis	254	18079	14.19	[12.53,16.08]
Dry mouth	135	18932	7.16	[6.04,8.48]
Oral pain	102	6065	16.86	[13.85,20.51]
Abdominal discomfort	94	53284	1.76	[1.44,2.16]
Abdominal pain upper	86	54609	1.57	[1.27,1.94]
Constipation	76	60471	1.25	[1.00,1.57]
Dysphagia	63	22507	2.8	[2.18,3.58]
General disorders and administration site conditions				
Death	635	242546	2.67	[2.47,2.89]
Fatigue	586	231230	2.58	[2.37,2.80]
Asthenia	252	97771	2.59	[2.29,2.94]
Pyrexia	198	96201	2.06	[1.79,2.37]
Malaise	142	118201	1.2	[1.02,1.41]
Disease progression	128	31993	4.01	[3.37,4.77]
Drug intolerance	93	38160	2.44	[1.99,2.99]
Illness	86	42016	2.05	[1.65,2.53]
Thirst	51	5166	9.87	[7.49,13.01]
Mucosal inflammation	50	6944	7.2	[5.45,9.51]
Metabolism and nutrition disorders				
Hyperglycaemia	1019	8224	130.84	[122.38,139.87]
Decreased appetite	380	65485	5.89	[5.32,6.52]
Dehydration	152	31013	4.92	[4.19,5.77]
Diabetes mellitus	146	19056	7.69	[6.53,9.06]
Diabetic ketoacidosis	74	6459	11.47	[9.11,14.43]
Feeding disorder	69	6461	10.69	[8.43,13.55]
Skin and subcutaneous tissue disorders				
Rash	1021	131175	8.16	[7.66,8.70]
Pruritus	163	106855	1.53	[1.31,1.78]
Alopecia	139	65402	2.13	[1.80,2.51]
Dry skin	80	56717	1.41	[1.13,1.75]
Urticaria	67	44074	1.52	[1.19,1.93]
Investigations				
Blood glucose increased	823	41650	20.59	[19.19,22.10]
Weight decreased	349	81968	4.31	[3.88,4.79]
Blood creatinine increased	76	17093	4.45	[3.55,5.57]
Blood glucose abnormal	66	5090	12.97	[10.17,16.55]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Malignant neoplasm progression	218	32496	6.76	[5.91,7.73]
Breast cancer metastatic	87	2644	32.96	[26.61,40.83]
Metastases to liver	61	5170	11.8	[9.16,15.20]
Immune system disorders				
Hypersensitivity	100	58054	1.72	[1.41,2.10]
Nervous system disorders				
Taste disorder	87	10498	8.3	[6.72,10.25]
Psychiatric disorders				
Eating disorder	63	6157	10.23	[7.98,13.12]
Eye disorders				
Vision blurred	50	32420	1.54	[1.17,2.03]

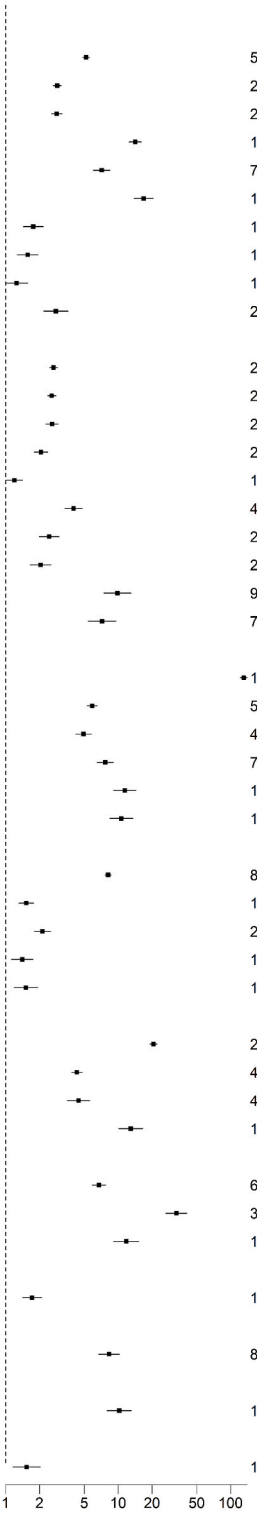

Fig. 2. Reporting odds ratios (ROR) with 95% Cl for all positive alpelisib-related AEs in at least 50 cases. CI, confidence interval; N, number of cases of total AEs associated with the target drug; ROR, reporting odds ratio; n, number of cases with suspected AEs associated with the target drug.

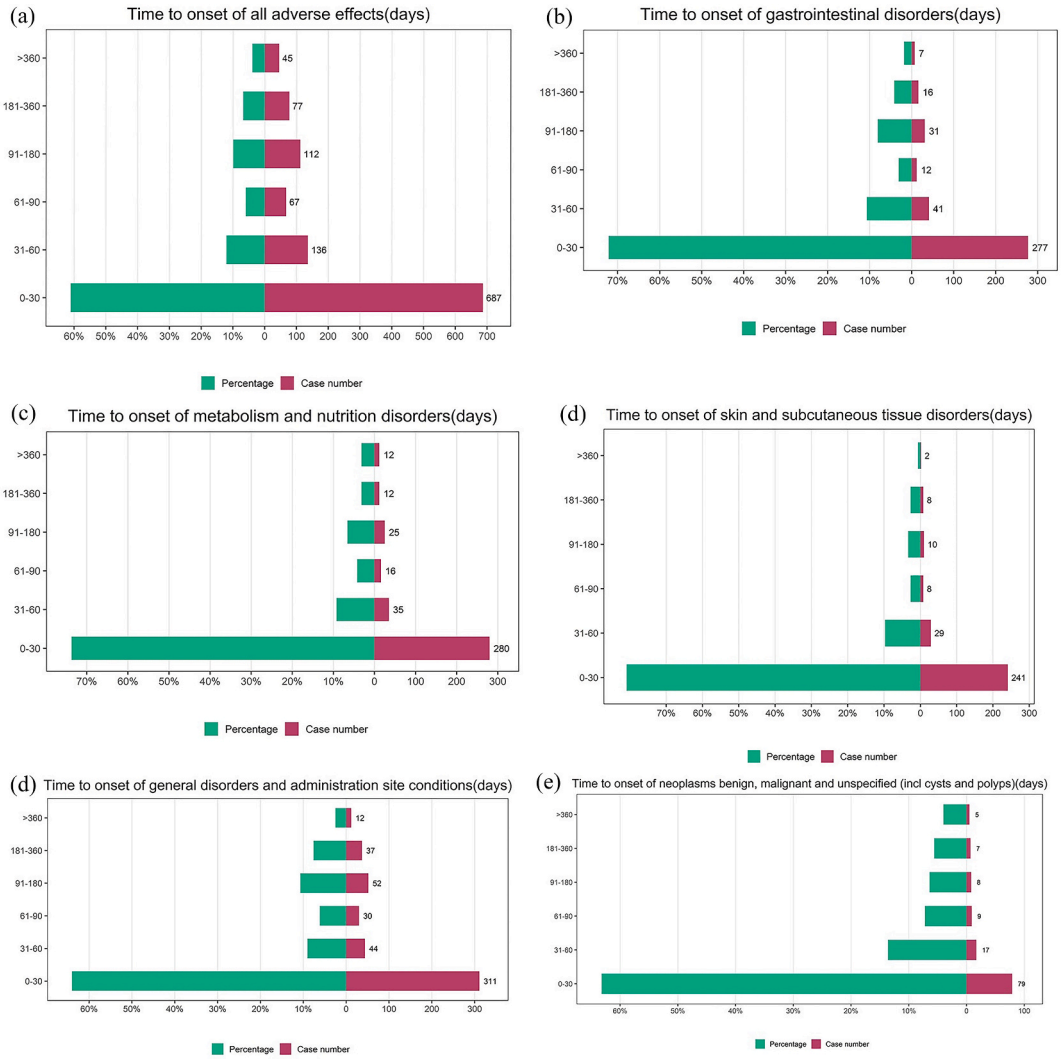

Fig. 3. Time to onset of adverse effects of alpelisib. (a) Time to onset of all adverse effect of alpelisib; (b) Time to onset of gastrointestinal disorders of alpelisib; (c) Time to onset of metabolism and nutrition disorders of alpelisib; (d) Time to onset of skin and subcutaneous tissue disorders of alpelisib; (e) Time to onset of general disorders and administration site conditions of alpelisib; (f) Time to onset of neoplasms benign, malignant and unspecified (incl cysts and polyps) of alpelisib.

clinicians to be vigilant about time of onset, proactively recognize and prevent adverse events, and take timely and effective measures.

Although our study was based on a real data mining strategy for the FAERS database, the pharmacovigilance database had some inherent limitations. First, since the reporting sources of the FAERS database are mainly from Europe and the United States, with less data from populations in other continents, there may be racial differences in the results of the study compared with those in other continents, but the mining of large samples is still informative for the safe use of medication in the clinic. Second, because FAERS is a spontaneous AE reporting system, it is inevitable that there will be omissions, underreporting and inaccurate reporting, all of which may bias the study results. Finally, although the ROR algorithm is highly sensitive, all signal detection results can only suggest correlation at the statistical level, and the signal intensity can only represent the relative risk magnitude. Therefore, further studies, such as experimental explorations, clinical trials, and case-control studies, are needed to confirm the existing results.

4. Conclusion

Our study provided an updated analysis between alpelisib and AEs based on real-world safety data from a large sample. Close attention should be paid to AEs with meaningful real-world signals (constipation, dysphagia, diabetic ketoacidosis, feeding disorder, urticaria, eye disorders and vision blurred) that are not listed in the FDA specification. Analysis of the timing of AEs indicated that most patients developed them within 30 days of alpelisib treatment. Our findings may improve the understanding of alpelisib-related toxicity and provide a meaningful insight for healthcare practitioners to reduce the risk of AEs via post-marketing safety assessments.

5. Methods

5.1. Study design and data source

The FAERS database is one of the largest pharmacovigilance repositories, virtually covering a worldwide population. We performed an observational, retrospective disproportionality analysis of FAERS. According to the FDA approval time of alpelisib, all reports recorded in FAERS covering the period from the second quarter of 2019 (Q2) to the fourth quarter of 2022 (Q4).

5.2. Data extraction and descriptive analysis

The FAERS database consisted of seven datafiles: patient demographic information (DEMO), drug information (DRUG), adverse event information (REAC), patient outcome information (OUTC), report source information (RPSR), drug therapy date information (THER), and drug indication (INDI). All data were imported into SAS software (v9.4; America), and the deduplication process was performed before statistical analysis. The primary ID was the primary link field (primary key) between different data files, and the case ID was chosen as the key filter in our study to remove duplicate records (18). We identified cases using drug name (alpelisib, BYL719, piqray, NVP-BYL719) in the DRUG file, and chose the role_cod as PS (Primary suspected). AEs in FAERS are coded using the preferred PT from standardized Medical Dictionary for Regulatory Activities (MedDRA), which contains 27 SOCs. Further, a PT could be linked to more than one the SOC in MedDRA. Accordingly, MedDRA 26.0 was used to classify AEs in each report to the corresponding the SOC levels in SAS 9.4. All the PTs below the SOC in the FAERS database were included in our study.

Subsequently, the clinical characteristics of reports were described in detail, if the data were available, including gender, age, weight, reporting area, reporters and outcomes, etc. It is worth noting that we also analyzed the time to onset of alpelisib-associated AEs. A flow diagram including the multi-step process of data extraction, processing, and analysis was shown in Fig. 1.

5.3. Statistical analysis

We used the reporting odds ratio (ROR), one of the algorithms used in disproportionality analysis was based on the 2×2 table calculation principle, to assess suspected AEs of alpelisib. All AEs with at least fifty reports were selected to reduce the likelihood of false positives. We then performed signal strength of reports of alpelisib at both PT and SOC levels in FAERS database, and a positive signal was considered when the lower limit of the ROR 95% confidence interval (CI) exceeded one.

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Data availability statement

The data can get from “Li, Hang (2023), “alpelisib AEs”, Mendeley Data, V1, doi: 10.17632/wzx5g42c6s.1”.

CRediT authorship contribution statement

Yun Li: Data curation. **Hang Li:** Writing – original draft. **Zhongyuan Xiang:** Project administration.

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.

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