Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Safety and ragional differences of Isatuximab-pomalidomide-dexamethasone combination in relapsed/refractory multiple myeloma: an external validation using FAERS and Lecheng real-world database

Qiao-Qiao Chen
Ruijin-Hainan Hospital, Shanghai Jiao Tong University School of Medicine (Hainan Boao Research Hospital)

Jian-Hua You
Ruijin-Hainan Hospital, Shanghai Jiao Tong University School of Medicine (Hainan Boao Research Hospital)

Zi-Yin Huang
Ruijin-Hainan Hospital, Shanghai Jiao Tong University School of Medicine (Hainan Boao Research Hospital)

Xin-Xin Chen
Ruijin-Hainan Hospital, Shanghai Jiao Tong University School of Medicine (Hainan Boao Research Hospital)

Li-Qun Zhang
zlq40599@rjh.com.cn

Ruijin Hospital

Research Article

Keywords:

Posted Date: November 13th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11525112/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Safety and ragional differences of Isatuximab-pomalidomide-dexamethasone combination in relapsed/refractory multiple myeloma: an external validation using FAERS and Lecheng real-world database

Qiao-Qiao Chen[1], Jian-Hua You[3, 4], Zi-Yin Huang[1], Xin-Xin Chen[1], Li-Qun Zhang[2※]

1 Department of Pharmacy, Ruijin-Hainan Hospital, Shanghai Jiao Tong University School of Medicine (Hainan Boao Research Hospital), Qionghai 571400, China;

2 Department of Pharmacy, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200025, China;

3 Department of Hematology, Ruijin-Hainan Hospital, Shanghai Jiao Tong University School of Medicine (Hainan Boao Research Hospital), Qionghai 571400, China

4 Shanghai Institute of Hematology, State Key Laboratory of Medical Genomics, National Research Center for Translational Medicine at Shanghai, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200020, China.

Correspondence: Li-Qun Zhang (zlq40599@rjh.com.cn)

ABSTRUCT

Isatuximab approved by FDA in 2020 for the treatment of relapsed and refractory multiple myeloma (RRMM), although ICARIA-MM trial established its efficacy, leaving gap in different regional healthcare systems and reporting methodologies. This study investigated the AE profile of Isatuximab combined with pomalidomide-dexamethasone (Isa-Pd), focusing on safety of Isa-Pd, and regional differences between Lecheng and French in FAERS (FR). Lecheng data (2022Q3–2024Q2) were extracted from a prospective observational real-world study in China (IsaFiRsT), while FAERS reports (2020Q1–2025Q4) were obtained from the FDA Adverse Event Reporting System database. AE terms were standardized using MedDRA, and data mining used ROR, PRR, BCPNN, and MGPS algorithms. Our study divided into 2 parts: 1. Analysis all Isa-Pd-related data in FAERS and Lecheng. 2. Comparing the database of French in FAERS with Lecheng to get regional differences. A total of 507 AE reports were analyzed, with 200 reports from Lecheng and FR used for regional comparison. Strong overall signals included infections and infestations, blood/lymphatic system disorders, investigations, and cardiac disorders. Beyond known hematological toxicities, this study identified unexpected risk signals, including cardiac failure, hypertension, hypokalemia, and *Pneumocystis jirovecii* pneumonia, which are not fully characterized in current prescribing information. No specific fatal risk was attributed to Isa-Pd. Regional differences were observed between Lecheng and FR: Lecheng group had more males (Lecheng 62.5% *vs* FR 48.21%), and lderly patients(≥65 years: Lecheng 70.45% *vs* FR 58.93%). AEs reported group show difference, all data in Lecheng by physicians, and FR data reported almost equally by pharmacist (56.25%) and physician (42.86%). Lecheng shows frequent hospitalization (100%) in outcome, while FR showed a broader outcome spectrum (hospitalization 53.57%, Life-Threatening 12.50%, death 4.5%). Onset was shorter in Lecheng (Median Lecheng 9.50 *vs* FR 13.50), Lecheng AE signals concentrated in Investigations (Neutrophil count decreased, ROR=172.21; Platelet count decreased, ROR=22.75). FR group AE signals distributed across Blood

and lymphatic system disorders (Lymphopenia, ROR=58.15; Neutropenia, ROR=31.76), Infections and infestations (COVID-19, ROR=12.11), and Vascular disorders (Hypertension, ROR=18.28). These regional differences may be related to population variations, regional management, and distinct post-AE medication regimens. Crucially, by introducing a prospective local real-world cohort (Lecheng) as an external validation for FAERS, this study overcomes the inherent under-reporting biases of spontaneous systems. It comprehensively characterizes the Isa-Pd safety profile, uncovers unexpected risks, and provides robust pharmacological evidence for individualized safety monitoring and risk mitigation.

Keywords

Isatuximab; RRMM; adverse drug reaction; Real-world data analysis; FAERS

Introduction

Multiple myeloma (MM) is an end-stage differentiated plasma cell malignancies, associated with the presence of bone marrow infiltrations of clonal plasma cells and monoclonal proteins in serum and/or urine (An G, et al. 2025). The disease is typically accompanied by hyper-Calcemia, Renal insufficiency, Anemia, Bone diseases/lesions, and immune deficiency (CRAB). Current treatment modalities include hematopoietic stem cell transplantation and immunotherapies such as immunomodulatory drugs (IMiDs), monoclonal antibodies, and T-cell redirected therapies (bispecific antibodies and CAR-T cell therapy) (Bate A, et al. 1998). While these advances have improved outcomes, MM remains highly prone to relapse and difficult to cure, imposing a heavy burden on patients' lives. Epidemiological data from the Global Burden of Disease (GBD) 2021 study estimated 17,250 new MM cases and 12,984 deaths in China, with age-standardized incidence and mortality rates continuing to rise, particularly in males (Boissel N, et al. 2022). Once drug resistance occurs in patients after using IMiD and PI, the treatment options available for relapsed/refractory multiple myeloma (RRMM) are significantly limited (Chen W, et al. 2025).

Isatuximab (Isatuximab-irfc; Sarclisa) is an IgG1 monoclonal antibody that binds to the glycoprotein CD38 expressed on the surface of hematopoietic and tumor cells.

It was developed by Sanofi under license from Immunogen for the treatment of hematological malignancies, and approved by FDA in 2020 and receiving positive evaluation in EU for the treatment of RRMM(Chen Y, et al. 2021). Clinical research of Isatuximab is underway in several countries(Coffman K, et al. 2022; Dhillon S , 2020; Dimopoulos M, et al. 2025; Dou X, et al. 2025; Encinas C, et al. 2025; Fedyk ER, et al. 2020) and Hainan Boao Lecheng International Medical Tourism Pilot Zone Hainan Free Trade Port (Chen W, et al. 2025). In 2024, the FDA approved Isa-VRd (Isatuximab with lenalidomide, bortezomib and dexamethasone) for new diagnostic MM patients as best standard of care (Encinas C, et al. 2025; Fedyk ER, et al. 2020). Previous evidences (Coffman K, et al. 2022; Frerichs KA, et al. 2018) showed that Isatuximab could prolong median progression-free survival (mPFS) and improve overall response rate (ORR) in patients with RRMM. However these trail may not fully reflect the complex clinical landscape and safety profiles of real-world RRMM populations.

Currently, prospective real-world safety data for Isa-Pd, particularly in Asian populations, remain scarce. Moreover, while FAERS serves as a valuable pharmacovigilance tool, which limited by under-reporting and reporting biases. To address these gaps, this study uniquely introduces the Hainan Boao Lecheng prospective real-world cohort (IsaFiRsT study) (Chen W, et al. 2025) as an external validation for the FAERS database. We aimed to systematically compare the safety profiles and regional disparities between France and Lecheng (China), and crucially, to identify unexpected AEs not fully characterized in current prescribing information, thereby providing robust pharmacological evidence for individualized safety monitoring.

Methods

Data source

The data source of this paper consists of two parts: Lecheng indult drug medicine devices platform and FDA Adverse Event Reporting System (FEARS). The keywords "SARCLISA", "Isatuximab" and "isatuximab-irfc" were searched in FAERS databases. we extracted all recorded reports for the period from 2020Q1 to 2025Q4. Lecheng indult drug medicine devices platform We collected the adverse reaction records of 24 patients who used Isatuximab in Lecheng Specialized Drug and Medical Device Traceability Platform from 2022Q3 to 2024Q2 (Dimopoulos M, et al. 2025). Among them, there were 64 treatment-related serious adverse events (TRSAE). Cases where treatment was terminated due to patient progression or adverse events after drug use were not recorded. New adverse reactions were obtained after comparing with the instructions. The AE data used the names and grades of the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (1-5). Select the same fields of data downloaded from Lecheng indult drug medicine devices platform and FEARS database for translation and integration. Setting the primary suspected drug as "Isatuximab", and the medication record also includes “Pomalidomide” and “Dexamethasone”. After first analysis all data, we choosing the reporter country as “France”, compare them with Lecheng data (Figure 1). Given that the FAERS constitutes a publicly accessible and anonymized dataset, the requirement for institutional review board approval and informed consent has been waived. Lecheng data came from a prospective observational real-world study (IsaFiRsT), ethical approval for this study was approved by the Ethics Committee of Shanghai Jiaotong University School of Medicine, Ruijin-Hainan Hospital (No. 20250113). Written informed consent was obtained from all patients in the Isa-Pd cohort.

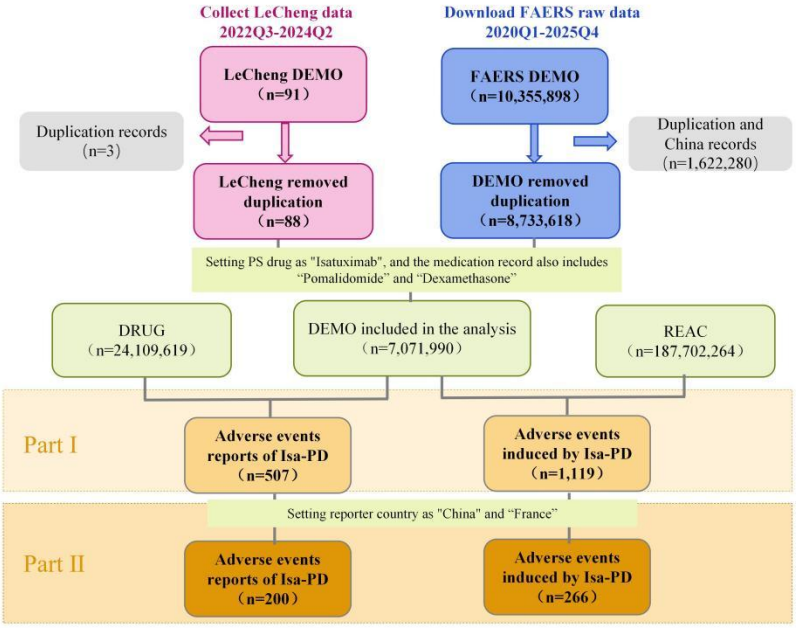


Fig. 1. Flow diagram of the data extraction and analysis process for “Isa-PD”-ralated AEs from the FAERS and Lecheng database. Data collected consists FAERS and LeCheng: 1. From 2020Q1 to 2025Q4, 10,355898 FAERS DEMO have been download, after duplication and China records(n=1,622,280), get FAERS unique DEMO (n=8,733,618). 2. From 2022Q3 to 2024Q2, 91 LeCheng DEMO has been collect, After duplication records (n=3), get unique LeCheng DEMO (n=88). Involving these two parts and setting combined medication regimen as “Isa-PD”("ISATUXIMAB" index 'POMALIDOMIDE' and 'DEXAMETHASONE'), then got Combined DEMO (n=7,071,990). DRUG data (n=24,109 619) was merged with Combined DEMO, corresponding to 507 reports. REAC data (n=187,702,264) was merged with Combined DEMO, corresponding to 1,119 AEs. Limited the reporter country as "China" and“France”, we finally got 200 reports (266 AEs).

Data cleaning

The data in Lecheng indult drug medicine devices platform was strictly compounded and intergrated by two person, delete duplicate and possibly irrelevant events. The present study was conducted in strict accordance with the FDA official website guidance document for data cleaning. We selected the PRIMARYID, CASEID, and FDA_DT fields from the DEMO table and sorted the reports using CASEID, FDA_DT, and PRIMA RYID. For reports with the same CASEID, we kept

the report with the largest FDA_DT value. Similarly, for both CASEID and FDA_DT, we retained the report with the largest PRIMARYID value (Tan CR, et al. 2025).

MedDRA dictionary application

The Medical Dictionary for Regulatory Activities (MedDRA) is used to standardize the preferred terms (PTs) of the descriptive language in the adverse reaction reports of Isatuximab obtained through data cleaning. Delete reports with obvious error information that are not related to the drug, such as product issues, various injuries, poisoning and operational complications, social environment, various surgeries and medical procedures, and various congenital familial genetic diseases. MedDRA contains approximately 120,000 terms, each with a unique 8-digit Arabic numeral code. The terminology is organized into five hierarchical levels: Low-Level Terms (LLTs), PTs, High-Level Terms (HLTs), High-Level Group Terms (HLGTs), and System Organ Classes (SOCs). The SOCs and PTs from the 27.1 version for the MedDRA dictionary were obtained for subsequent analysis.

Statistical analysis

The sources of AE collected by FDA are diverse, some countries report according to region, and the data need to be merged with the same country. Statistical analysis was conducted using SAS9.4 software. In this study, the reporting odds ratio (ROR) method, the proportional reporting ratio (PRR) method (van de Donk NWCJ, et al. 2018) the Bayesian confidence interval progressive neural network (BCPNN) method (van Puijenbroek EP, et al. 2002) and multi-item gamma Poisson shrinker (MGPS) method (Vassilopoulos S, et al. 2022) were uesd in combination with data mining to attempt to reduce the result bias of single algorithm. These four methods were used proportional imbalance method to detect the adverse reaction signals. The equation and criteria of four algorithms were summarized in Table 1. The results of signal detection by the lower limit of the PRR confidence interval method are almost consistent with those detected by the ROR method. Generally, the British Medicines and Healthcare Products Regulatory Agency (MHRA) comprehensive standard method is commonly used for signal detection.

Table 1. Methods, formulas, and thresholds for Reporting Odds Ratio (ROR),

Proportional Reporting Ratio (PRR), Bayesian Confidence Propagation Neural Network (BCPNN), and Muti-item Gamma Poisson Shrinker (MGPS). (a) Count of reports featuring both the specified drug and target adverse events; (b) number of reports involving other adverse drug events alongside the specified drug; (c) reports of target adverse drug events involving other drugs; (d) reports encompassing other drugs and non-targeted adverse drug events.

95% CI: 95% confidence interval; N: number of reports; $\chi 2$: chi-squared; IC: information component; IC025: lower limit of 95% CI of the IC; E (IC): IC expectations; V(IC): variance of IC; EBGM05: lower limit of 95% CI of EBGM.

Algorithms	Equation	Criteria
ROR	$\mathrm{ROR} = \frac{(a/c)}{(b/d)}$ $\mathrm{SE}(\ln\mathrm{ROR}) = \sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}$ $95\%\mathrm{CI} = \mathrm{e}^{\ln(\mathrm{ROR}) \pm 1.96\sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}}$	a ≥ 3, lower limit of 95% CI > 1
PRR	$\mathrm{PRR} = \frac{a(c+d)}{c(a+b)}$ $\mathrm{SE}(\ln\mathrm{PRR}) = \sqrt{\frac{1}{a}+\frac{1}{c}-\frac{1}{a+b}-\frac{1}{c+d}}$ $95\%\mathrm{CI} = \mathrm{e}^{\ln(\mathrm{PRR}) \pm 1.96\sqrt{\frac{1}{a}+\frac{1}{c}-\frac{1}{a+b}-\frac{1}{c+d}}}$ $x^2 = \frac{(ad-bc)^2(a+b+c+d)}{(a+b)(a+c)(c+d)(b+d)}$	a ≥ 3, PRR ≥ 2, x^2 ≥ 4
BCPNN	$\mathrm{IC} = \log_2 \frac{a(a+b+c+d)}{(a+c)(a+b)}$ $\mathrm{IC}-2\mathrm{SD} = \mathrm{E(IC)} - 2\sqrt{\mathrm{V(IC)}}$	IC − 2SD > 0
MGPS	$\mathrm{EBGM} = \frac{a(a+b+c+d)}{(a+c)(a+b)}$ $95\%\mathrm{CI} = \mathrm{e}^{\ln(\mathrm{EBGM}) \pm 1.96\sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}}$	EBGM05 > 2

Result

Descriptive characteristics associsted with Isa-Pd

The clinical features of the cases and the baseline characteristics of the patients who received treatment with Isa-Pd are summarized (see Supplementary Table S1 online). Male (N=265) accounted for 52.27% of the patients, and the most common age was greater than 65 (N=293) accounted for 57.79% of the patients. This treatment had the highest proportion of Adverse events in 2023 (37.87%, N=192). Mostly AE were reported by physician (70.22%, N =356). In Geographically, this treatment was most widely used in Europe (42.60%, N=216), followed by Asia (34.71%, N=176), then North America (11.05%, N=56), Oceania (6.90%, N=35) and South America (4.73%, N=24). Reporting country including France (22.09%, N=112), followed by Lecheng (17.39%, N=88), Japan (14.99%, N=76), the United States (10.06%, N=51) and Australia (6.90%, N=35). Most of the outcomes will lead to Hospitalization accounted for 64.10% of the patients (N=325). The majority of patients who treat with Isa-Pd, the TTO of AE occurred within 30 days (Median: 13 days (IQR: 4.50—67.00) (see Supplementary Fig. S1 online).

Signal values of Isa-Pd-related AEs in SOCs and PTs level

We found that Isa-Pd related AEs were distributed in 23 organ systems (see Fig. 2 and Supplementary Table S2 online). There were 4 significant SOCs that met four calculation criteria at the same time (p-value<0.0001), including Infections and infestations (19.03%, N=213, ROR 3.93, PRR 3.37, IC 1.75, EBGM 3.37), Blood and lymphatic system disorders (16.09%, N=180, ROR 10.98, PRR 9.38, IC 3.23, EBGM 9.37), Investigations (11.80%, N=132, ROR 2.21, PRR 2.07, IC 1.05, EBGM 2.07), Cardiac disorders (4.11%, N=46, ROR 2.17, PRR 2.12, IC 1.08, EBGM 2.12).

At PTs level, there were 24 significant PTs met four calculation criteria at the same time (p-value<0.0001). The top 10 case reports of PTs were Neutropenia (5.99%, N=67), Neutrophil count decreased (5.81%, N=65), Pneumonia (14%, N=24), Platelet count decreased (2.14%, N=24), Pyrexia (1.97%, N=22), Anaemia (1.88%, N=21), Febrile neutropenia (1.79%, N=20), Thrombocytopenia (1.79%, N=20), Disease progression (1.43%, N=16), Infusion related reaction (1.34%, N=15). The signal values detail in Fig. 3 and Supplementary Table S3 online.

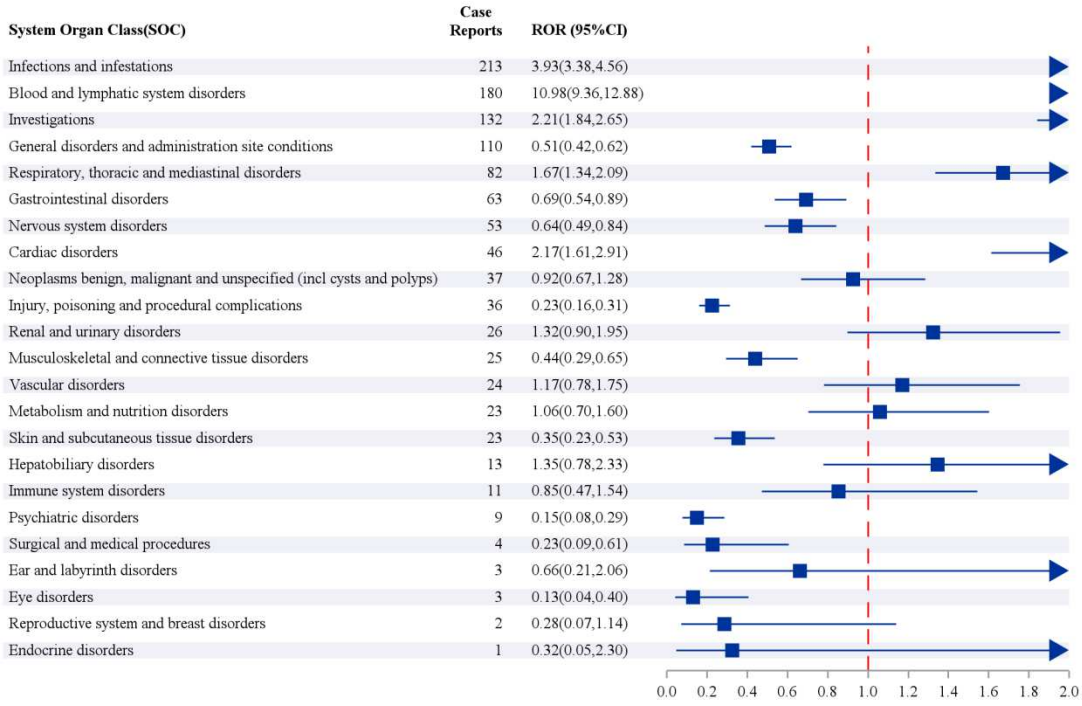


Fig. 2. Signal strength of adverse events associated with Isa-Pd across SOCs. 95% CI = 95% confidence interval.

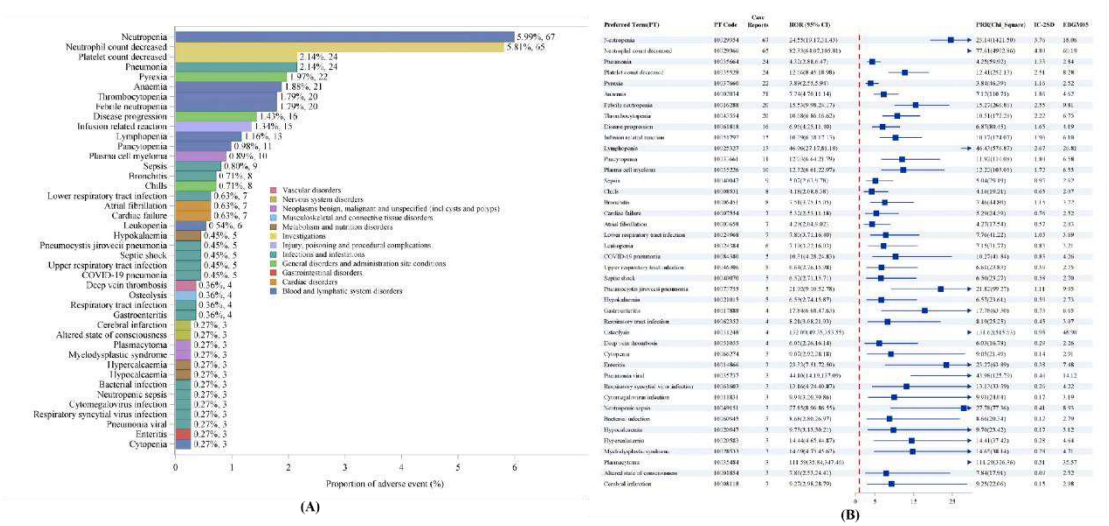
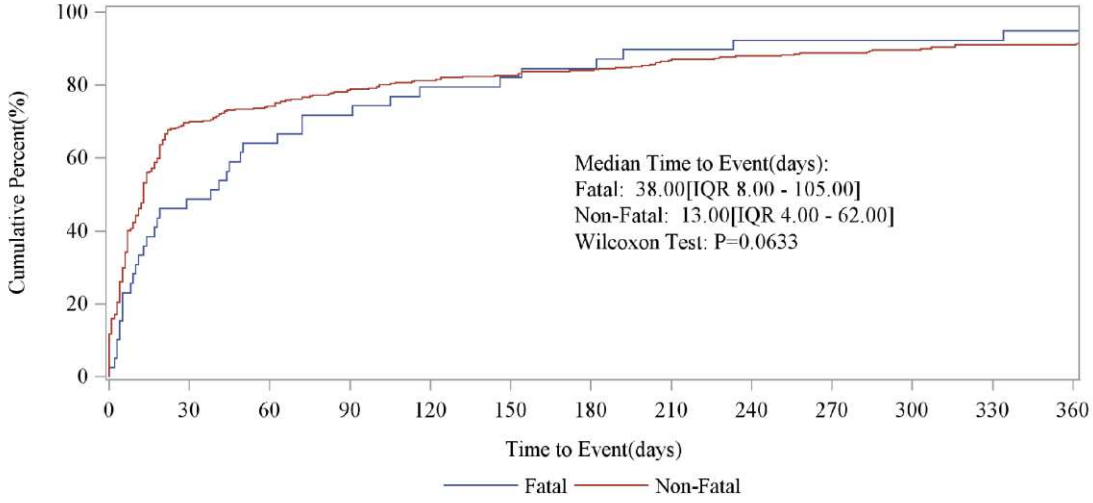


Fig. 3. Signal strength of PTs for adverse events associated with Isa-Pd. (**A**)shows top 50 PTs by Frequency for adverse events and their belonging of SOC. (**B**)displays the results of disproportionality analysis by ROR, PRR, BCPNN and MGPS.

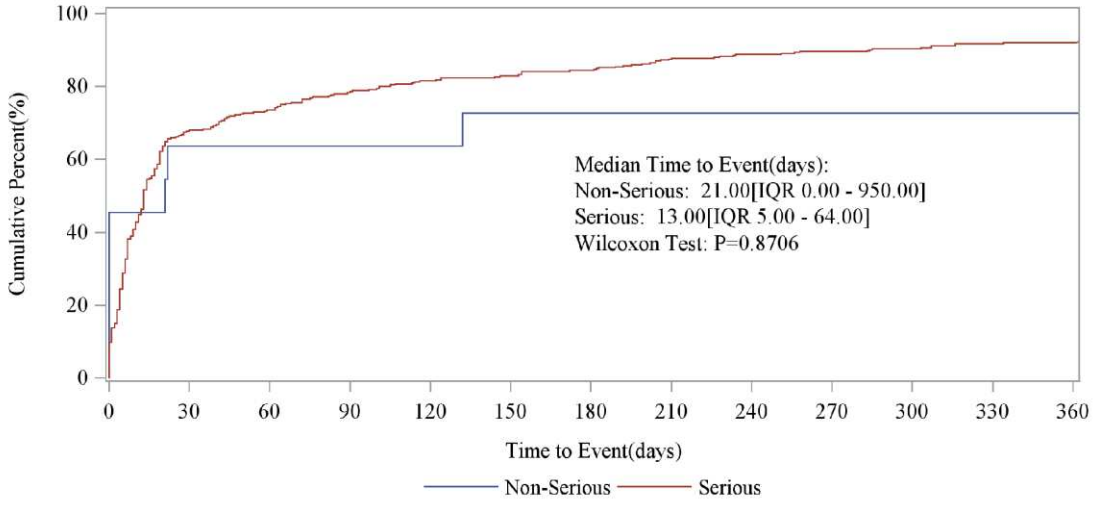
Positive signal strength and time to onsets of Isa-Pd-related SAEs

SAEs occurred earlier than Non-SAEs after the start of treatment of Isa-Pd (13 days (IQR 5.00—64.00) *vs* 21 days (IQR: 0.00—950.00), *P*=0.8706) (Fig. 4B). AEs associated with Isa-Pd therapy were analyzed by four calculation criteria (Table 2 and Fig. 5), most of AEs associated Isa-Pd are basically SAE reports. The characteristics met *P*<0.0001 are as follows. At the PT level, the most prominent SAEs were

haematological toxicities, including Neutrophil count decreased (N=64, ROR 68.60, PRR 64.58, IC 6.01, EBGM 64.33), Neutropenia (N=66, ROR 17.72, PRR 16.70, IC 4.06, EBGM 16.68), Lymphopenia (N=13, ROR 36.31, PRR 35.88, IC 5.16, EBGM 35.81), Thrombocytopenia (N=20, ROR 7.80, PRR 7.68, IC 2.94, EBGM 7.67), Febrile neutropenia (N=20, ROR 11.04, PRR 10.86, IC 3.44, EBGM 10.85), and Neutropenic sepsis (N=3, ROR 19.77, PRR 19.71, IC 4.30, EBGM 19.69). Infections were also highly frequent, including Pneumonia viral (N=3, ROR 32.01, PRR 31.92, IC 4.99, EBGM 31.86), COVID-19 pneumonia (N=5, ROR 7.44, PRR 7.41, IC 2.89, EBGM 7.41), Respiratory syncytial virus infection (N=3, ROR 11.99, PRR 11.96, IC 3.58, EBGM 11.95), Pneumocystis jiroveci pneumonia (N=5, ROR 15.64, PRR 15.57, IC 3.96, EBGM 15.55), Enteritis (N=3, ROR 17.09, PRR 17.05, IC 4.09, EBGM 17.03). In addition, Plasmacytoma (N=3, ROR 81.04, PRR 80.82, IC 6.33, EBGM 80.43) and Osteolysis (N=3, ROR 95.26, PRR 94.91, IC 6.56, EBGM 94.37) indicated some patients disease progression. Infusion related reaction (N=13, ROR 7.96, PRR 7.87, IC 2.98, EBGM 7.87), Chills (N=7, ROR 4.00, PRR 3.98, IC 1.99, EBGM 3.98) reflected acute infusion reactions. Cardiovascular events such as Deep vein thrombosis (N=4, ROR 4.39, PRR 4.38, IC 2.13, EBGM 4.38), Atrial fibrillation (N=7, ROR 3.13, PRR 3.12, IC 1.64, EBGM 3.12) and Cardiac failure (N=7, ROR 3.80, PRR 3.78, IC 1.92, EBGM 3.78) were also reported. At the SOC level, Blood and lymphatic system disorders (16.64%, N=179, ROR=8.22) and Infections and infestations (19.80%, N=213, ROR=3.50) showed the strongest signals among all SAEs.



(A)



(B)

Fig. 4. Time to onset of Isa-Pd related AEs. (**A**)shows Fatal subgroup (**B**) shows Serious subgroup

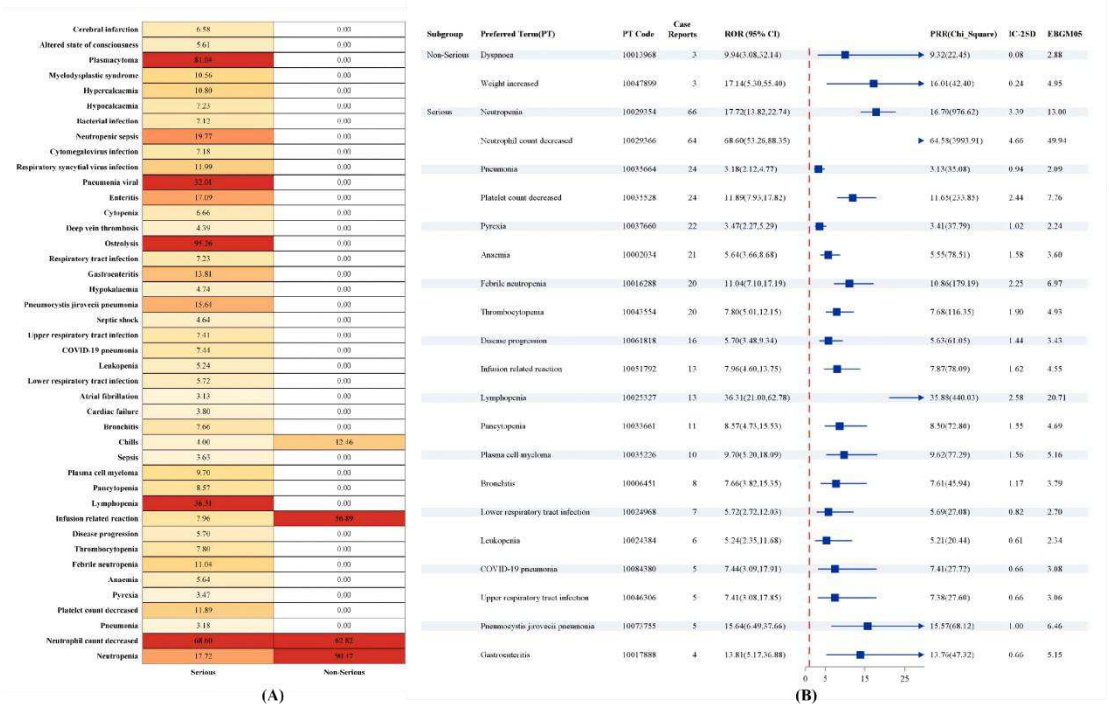


Fig. 5. Positive signal strength of Non-/Serious adverse events associated with Isa-Pd. (**A**) presents the distribution of Top 50 PTs Across Different Non-/Serious adverse events by heatmap. (**B**) displays the results of disproportionality analysis by ROR, PRR, BCPNN and MGPS. IQR, interquartile range.

Table 2. Signal strength of SAEs of Isa-Pd at the SOC level in FAERS and Lecheng database.

SOC	n(%)	*P*-Value	ROR(95% CI)	PRR(χ^2)	IC(IC025)	EBGM (EBGM05)
Infections and infestations	213(19.80)	<.0001	3.50(3.01-4.07)*	3.00(304.89)*	1.59(1.36)*	3.00(2.59)*
Blood and lymphatic system disorders	179(16.64)	<.0001	8.22(7.00-9.65)*	7.02(945.98)*	2.81(2.53)*	7.02(5.98)*
Investigations	124(11.52)	<.0001	1.96(1.63-2.36)*	1.85(51.57)*	0.89(0.60)*	1.85(1.53)
General disorders and administration site conditions	101(9.39)	<.0001	0.58(0.47-0.71)	0.62(28.06)	-0.69(-0.99)	0.62(0.50)
Respiratory, thoracic and mediastinal disorders	74(6.88)	0.0041	1.41(1.11-1.79)*	1.38(8.22)	0.47(0.11)*	1.38(1.09)
Gastrointestinal disorders	59(5.48)	0.0022	0.67(0.51-0.86)	0.68(9.41)	-0.55(-0.93)	0.68(0.53)
Nervous system disorders	49(4.55)	<.0001	0.57(0.43-0.76)	0.59(15.20)	-0.76(-1.17)	0.59(0.44)
Cardiac disorders	45(4.18)	0.0021	1.59(1.18-2.14)*	1.57(9.44)	0.65(0.19)*	1.57(1.16)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	37(3.44)	0.0119	0.66(0.47-0.91)	0.67(6.32)	-0.58(-1.04)	0.67(0.48)
Injury, poisoning and procedural complications	29(2.70)	<.0001	0.26(0.18-0.38)	0.28(59.07)	-1.83(-2.33)	0.28(0.19)
Renal and urinary disorders	26(2.42)	0.9088	1.02(0.69-1.51)*	1.02(0.01)	0.03(-0.53)	1.02(0.69)

Musculoskeletal and connective tissue disorders	25(2.32)	<.0001	0.43(0.29-0.63)	0.44(18.89)	-1.19(-1.73)	0.44(0.30)
Vascular disorders	24(2.23)	0.9137	1.02(0.68-1.53)*	1.02(0.01)	0.03(-0.55)	1.02(0.68)
Metabolism and nutrition disorders	23(2.13)	0.5853	0.89(0.59-1.35)	0.89(0.30)	-0.16(-0.75)	0.89(0.59)
Skin and subcutaneous tissue disorders	22(2.04)	0.0023	0.52(0.34-0.80)	0.53(9.30)	-0.91(-1.48)	0.53(0.35)
Hepatobiliary disorders	13(1.21)	0.9854	0.99(0.58-1.72)	0.99(0.00)	-0.01(-0.78)	0.99(0.58)
Immune system disorders	11(1.02)	0.6341	0.87(0.48-1.57)	0.87(0.23)	-0.21(-1.03)	0.87(0.48)
Psychiatric disorders	9(0.84)	<.0001	0.13(0.07-0.25)	0.14(51.82)	-2.86(-3.65)	0.14(0.07)
Surgical and medical procedures	4(0.37)	0.0004	0.20(0.07-0.53)	0.20(12.78)	-2.30(-3.35)	0.20(0.08)
Ear and labyrinth disorders	3(0.28)	0.6631	0.68(0.22-2.11)	0.68(0.45)	-0.56(-1.88)	0.68(0.22)
Eye disorders	3(0.28)	0.0002	0.15(0.05-0.48)	0.16(13.89)	-2.68(-3.78)	0.16(0.05)
Reproductive system and breast disorders	2(0.19)	0.0948	0.33(0.08-1.30)	0.33(2.79)	-1.61(-2.92)	0.33(0.08)
Endocrine disorders	1(0.09)	0.2077	0.25(0.03-1.76)	0.25(2.28)	-2.01(-3.37)	0.25(0.03)

*Indicates statistically significant signals in algorithm. SOC, system organ class; ROR, reporting odds ratio; CI, confidence interval; PRR, proportional reporting ratio; χ^2, chi-information component; IC, information component; IC025, the lower limit of 95% CI ofthe IC; EBGM, empirical Bayesian geometric mean; EBGM05, the lower limit of 95% CI of EBGM; -, the range of the 95% confidence interval.

Analysis of AEs associated with Isa-Pd Fatal outcomes

TTO of Isa-Pd-related AEs found that Non-fatal AEs occurred earlier than fatal AEs after the first treatment of Isa-Pd (13 days (IQR 4.00—62.00) *vs* 38 days (IQR: 8.00—105.00)), while the faltal and Non-fatal AEs have no significant association (*P*=0.0633) (Fig. 4A). The volcano plot shows that non-fatal outcomes in patients were mainly associated with Neutrophil count decreased, whereas fatal outcomes were primarily associated with Disease progression and Plasma cell myeloma (Fig. 6). However, the Log_2 ROR (Range:–1.8, 8.0) and $-log_{10}$ *P*-value (Range: 0.3, 5.2) for both fatal and non-fatal events, with completely overlapping distributions. This indicates that over all of PTs, no single PT could discriminate between fatal and non-fatal outcomes based on signal strength or statistical significance. Which means events leading to fatal and non-fatal outcomes exhibited equivalent signal intensities at the detection level.

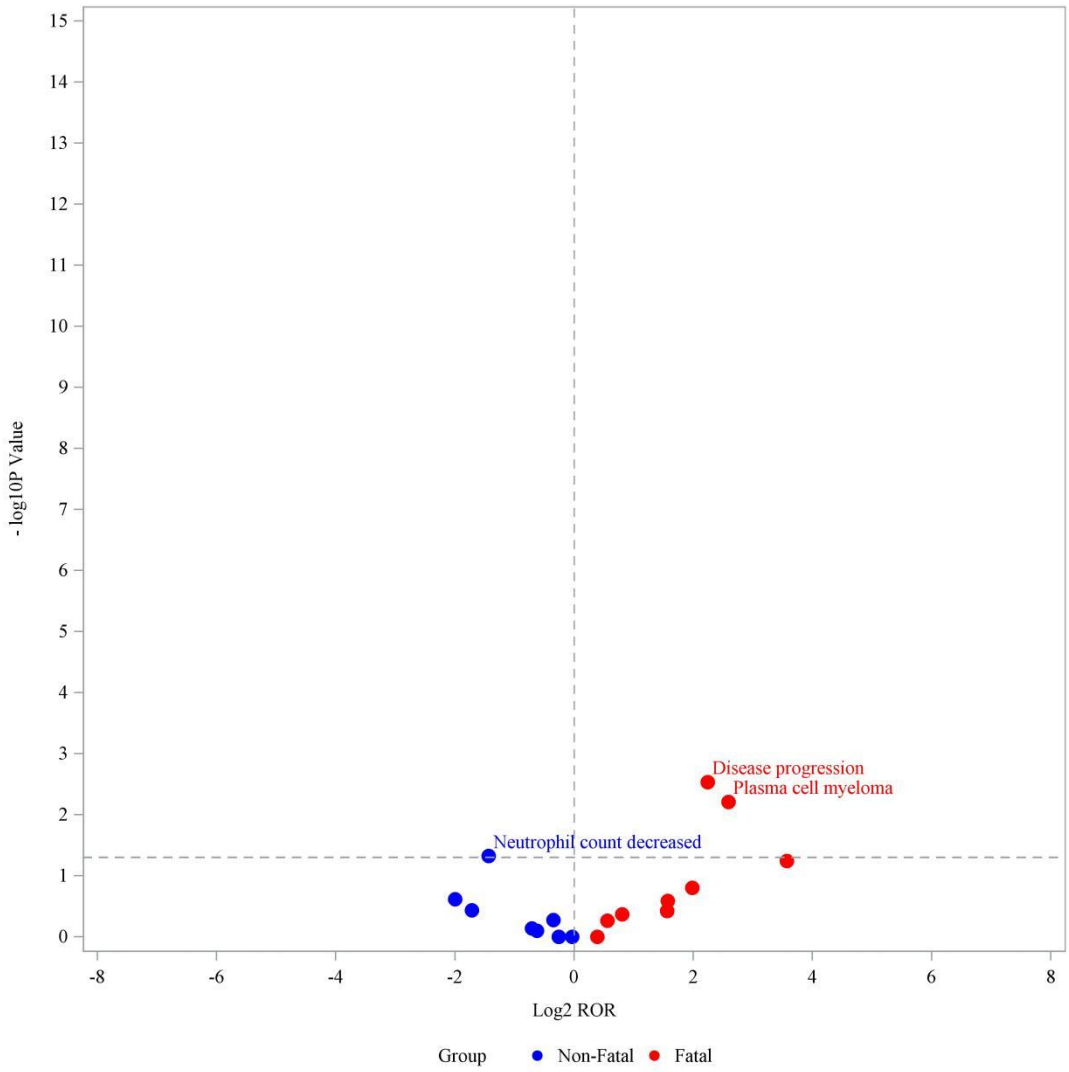


Fig. 6. Volcano Plot of fatal factors associated with Isa-Pd. The results of disproportionality analysis by ROR, PRR, BCPNN and MGPS. The X-axis represents the logarithm of the p-value based on Fisher's exact test (-log10P), and the Y-axis represents the negative logarithm of the ROR (log2ROR). Dots represent fatal factors.

Unexpected PTs

The entire list of 36 unexpected PTs and their signal values associated with Isa-Pd (p-value<0.0005) can be found as Supplementary Table S4 online. There were 18 unexpected PTs met four calculation criteria at the same time, including Pyrexia (N=22), Disease progression (N=16), COVID-19 (N=16), Pancytopenia (N=11), Hypertension (N=11), Sepsis (N=9), Chills (N=8), Cardiac failure (N=7), COVID-19 pneumonia (N=5), Septic shock (N=5), *Pneumocystis jirovecii* pneumonia (N=5), Hypokalaemia (N=5), Gastroenteritis (N=4), Osteolysis (N=4), Neutropenic sepsis

(N=3), Hypercalcaemia (N=3), Myelodysplastic syndrome (N=3), Plasmacytoma (N=3).

Characteristics of Lecheng and France Differences in Isa-Pd

In these two groups of subjects (Lecheng, N=88; France, FR, N=112), there were significant differences in the clinical characteristics of AEs (Table 3). In terms of sex distribution, Lecheng group had a higher proportion of males (Lecheng 62.5% *vs* FR 48.21%), while the French group had 5.4% of cases with unspecified sex. Regarding age distribution, Lecheng group had a higher proportion of elderly patients (≥65 years: Lecheng 70.5% *vs* FR 58.9%), with a slightly lower median age than FR group (Lecheng 63.22 (53.00,78.00) years *vs* FR 67.30 (43.00,89.00) years). The sources of AE reporting also differed markedly: all AEs in Lecheng were reported by physicians (100%), whereas FR reports were primarily submitted by pharmacists (56.25%) and physicians (42.86%). With respect to AE outcomes, all cases in Lecheng resulted in hospitalization (100%), among which 6.8% were also classified as life-threatening. In FR, the proportion leading to hospitalization(53.57%), death (4.5%), disability (0.9%), and other serious medical events (57.14%), indicating a more diverse spectrum of outcomes. Regarding the time of AE occurrence, a grate proportion cases occurred within 30 days in Lecheng (95.45%, Median: 9.50 days). In contrast, FR showed a more dispersed(53.57%, Median: 13.50 days) and 11.6% occurred beyond 360 days.

Table 3. Characteristics of reports in Lecheng and France associated with Isa-Pd from 2020 Q1 to 2025 Q4.

Characteristics	Lecheng(N=88)	FR(N=112)	Total
Gender, n(%)			
Female	33(37.50)	52(46.43)	85(42.50)
Male	55(62.50)	54(48.21)	109(54.50)
Not Specified	0(0.00)	6(5.36)	6(3.00)
Age (Year), n(%)			
<18	0(0.00)	0(0.00)	0(0.00)
18-64	26(29.55)	37(33.04)	63(31.50)
≥65	62(70.45)	66(58.93)	128(64.00)
Not Specified	0(0.00)	9(8.04)	9(4.50)
Median(Min, Max)	63.22(53.00,78.00)	67.30(43.00,89.00)	65.42(43.00,89.00)
Reporter, n (%)			

Consumer	0(0.00)	1(0.89)	1(0.50)
Pharmacist	0(0.00)	63(56.25)	63(31.50)
Physician	88(100.0)	48(42.86)	136(68.00)
Outcome, n (%)			
Life-Threatening	6(6.82)	14(12.50)	20(10.00)
Hospitalization - Initial or Prolonged	88(100.0)	60(53.57)	148(74.00)
Disability	0(0.00)	1(0.89)	1(0.50)
Death	0(0.00)	5(4.46)	5(2.50)
Congenital Anomaly	0(0.00)	0(0.00)	0(0.00)
Required Intervention to Prevent Permanent Impairment/Damage	0(0.00)	0(0.00)	0(0.00)
Other serious medical events	0(0.00)	64(57.14)	64(32.00)
Adverse event occurrence time (days), n (%)			
0-30d	84(95.45)	60(53.57)	144(72.00)
31-60d	0(0.00)	4(3.57)	4(2.00)
61-90d	4(4.55)	5(4.46)	9(4.50)
91-120d	0(0.00)	3(2.68)	3(1.50)
121-150d	0(0.00)	0(0.00)	0(0.00)
151-180d	0(0.00)	3(2.68)	3(1.50)
181-360d	0(0.00)	6(5.36)	6(3.00)
>360d	0(0.00)	13(11.61)	13(6.50)
Median(Min,Max)	9.50(0.00,89.00)	13.50(0.00,786.00)	11.00(0.00,786.00)

SOCs and PTs Signal value of Lecheng and France Differences in Isa-Pd

To further investigate the differences in safety profiles, we compared the signal values between the Lecheng and FR cohorts at both the SOC and PT levels ($P < 0.0001$). Significant regional disparities were observed in the signal distribution patterns (Tables 4 and 5).

At the SOC level, the Lecheng cohort exhibited a highly concentrated signal exclusively within "Investigations" (24.81%, N=66, ROR 23.91, PRR 6.73, IC 2.75, EBGM 6.72). In stark contrast, the FR cohort displayed a broader and more dispersed signal distribution across three primary SOCs: "Blood and lymphatic system disorders" (23.31%, N=62, ROR 9.68, PRR 6.65, IC 2.73, EBGM 6.64), "Infections and infestations" (12.78%, N=34, ROR 4.25, PRR 3.63, IC 1.86, EBGM 3.62), and "Vascular disorders" (5.26%, N=14, ROR 3.14, PRR 2.98, IC 1.57, EBGM 2.97). At the PT level, this discrepancy became even more pronounced. The Lecheng signals were overwhelmingly driven by laboratory test abnormalities, particularly a

remarkably strong signal for "Neutrophil count decreased" (18.42%, N=49, ROR 172.21, PRR 76.88, IC 6.24, EBGM 75.79) and "Platelet count decreased" (6.39%, N=17, ROR 22.75, PRR 18.55, IC 4.21, EBGM 18.49). Additionally, "Anaemia" (2.63%, N=7, ROR 12.90, PRR 11.95, IC 3.58, EBGM 11.92) was reported within the blood disorder SOC. Conversely, the FR cohort demonstrated highly significant signals for specific clinical events rather than laboratory parameters. The most prominent signals in the FR group included "Lymphopenia" (4.89%, N=13, ROR 58.15, PRR 53.97, IC 5.73, EBGM 53.20) and "Neutropenia" (12.03%, N=32, ROR 31.76, PRR 26.23, IC 4.70, EBGM 26.05) under blood disorders, alongside "Hypertension" (3.38%, N=9, ROR 18.28, PRR 17.41, IC 4.12, EBGM 17.33) and "COVID-19" (2.63%, N=7, ROR 12.11, PRR 11.67, IC 3.54, EBGM 11.64).

Table 4. Signal strength of reports of Isa-Pd at the SOC level between Lecheng and FR.（*P*-value <0.0001）

SOC	n(%)	ROR(95% CI)	PRR(χ^2)	IC(IC025)	EBGM(EBGM 05)
Lecheng					
Investigations	66(24.81)	23.91(14.75-38.74)*	6.73(361.74)*	2.75(2.15)*	6.72(4.15)*
FR					
Infections and infestations	34(12.78)	4.25(2.92-6.17)*	3.63(68.20)*	1.86(1.21)*	3.62(2.49)*
Blood and lymphatic system disorders	62(23.31)	9.68(7.11-13.17)*	6.65(313.78)*	2.73(2.18)*	6.64(4.88)*
Vascular disorders	14(5.26)	3.14(1.82-5.43)*	2.98(18.85)*	1.57(0.61)*	2.97(1.72)*

*Indicates statistically significant signals in algorithm. 95% CI = 95% confidence interval, EBGM = empirical bayes geometric mean, EBGM05 = the lower limit of 95% CI of EBGM, IC = information component, IC025 = the lower limit of 95% CI of the IC, PRR = proportional reporting ratio, ROR = the reporting odds ratio, χ2 = chi-squared; -, the range of the 95% confidence interval.

Table 5. Signal strength of reports of Isa-Pd at the PT level between Lecheng and FR.（*P*-value <0.0001）

SOC	PT	n(%)	ROR (95% CI)	PRR (χ^2)	IC (IC025)	EBGM (EBGM05)
Lecheng						
	Neutrophil count decreased	49(18.42)	172.21(112.93-262.61)*	76.88(3643.82)*	6.24(4.41)*	75.79(49.70)*
	Platelet count					
Investigations	decreased	17(6.39)	22.75(13.39-38.65)*	18.55(284.22)*	4.21(2.47)*	18.49(10.88)*
Blood and	Anaemia	7(2.63)	12.90(5.95-27.93)*	11.95(70.54)*	3.58(1.26)*	11.92(5.50)*

lymphatic system disorders						
FR						
	Neutropenia	32(12.03)	31.76(21.64-46.61)*	26.23(776.29)*	4.70(3.34)*	26.05(17.75)*
Blood and lymphatic system disorders	Lymphopenia	13(4.89)	58.15(32.93-102.66)*	53.97(666.98)*	5.73(2.68)*	53.20(30.13)*
	Thrombocytopenia	7(2.63)	5.14(2.41-10.94)*	4.97(22.36)*	2.31(0.68)*	4.97(2.33)*
Vascular disorders	Hypertension	9(3.38)	18.28(9.34-35.80)*	17.41(138.94)*	4.12(1.78)*	17.33(8.85)*
Infections and infestations	COVID-19	7(2.63)	12.11(5.68-25.81)*	11.67(68.30)*	3.54(1.27)*	11.64(5.46)*

*Indicates statistically significant signals in algorithm. 95% CI = 95% confidence interval, EBGM = empirical bayes geometric mean, EBGM05 = the lower limit of 95% CI of EBGM, IC = information component, IC025 = the lower limit of 95% CI of the IC, PRR = proportional reporting ratio, ROR = the reporting odds ratio, SOC = system organ class, $\chi 2$ = chi-squared; -, the range of the 95% confidence interval.

Clinical implications and supportive care based on Lecheng Database

In the Lecheng Real World study (Dimopoulos M, et al. 2025), 95.8% of the patients who received Isa-Pd experienced adverse events (Grade ≥ 3: AE), which was higher than the 85.7% reported in the French IMAGE study (Dhillon S , 2020). This discrepancy is likely due to Lecheng's comprehensive full-cycle patient management (spanning pre-treatment assessment, prophylaxis, medication, and post-treatment care), which facilitated intensive monitoring and 100% physician-driven reporting. To manage severe hematological toxicities (e.g., neutropenia and thrombocytopenia), clinicians in the Lecheng cohort employed proactive supportive care strategies. Prophylactic administration of cytokines (e.g., G-CSF and thrombopoietin) is recommended for patients at risk of bone marrow suppression. Furthermore, certain traditional Chinese medicines (TCM) may serve as potential adjunctive options to standard cytokine therapies, such as Qijiao Shengbai Capsule, Diyu Shengbai Tablet, and Shengxuebao Mixture.

Regarding infection management, the incidence of severe infections in Lecheng was relatively lower than that in the FR cohort. Strict monitoring for diarrhea and infection risks was implemented prior to drug administration, with timely administration of antifungal, antiviral, and antibiotic therapies when necessary. Furthermore, strict adherence to pre-infusion prophylactic medications (e.g.,

acetaminophen and antihistamines) significantly reduced the probability of severe infusion-related reactions.Which accounting for only a minor proportion of AEs, compared to 8.7% in the ICARIA-MM trial[7].

Discussion

In this study, proportional imbalance analysis was employed to identify substantial risk signals for Isa-Pd, examining data across multiple levels. Based on the FAERS database and the Lecheng real-world cohort, the overall AEs of Isa-Pd in RRMM predominantly occurred in male and elderly patients. Most AEs were reported by physicians, with Europe accounting for the highest number of reports, and France and Lecheng ranking as the top two reporting regions. The majority of outcomes led to hospitalization. At the SOC level, AEs involved 23 organ systems, among which four significant SOCs met all four calculation criteria: Infections and infestations, Blood and lymphatic system disorders, Investigations, and Cardiac disorders. At the PT level, among 24 significant PTs meeting all four criteria simultaneously, the top 10 by reporting frequency included Neutropenia, Neutrophil count decreased, Pneumonia, and Infusion related reaction. Fatal AE analysis suggested that Isa-Pd poses no specific fatal risk; rather, progression to death was mostly associated with the patient's baseline immune status, comorbidities, and anti-infection ability. The profound hematological toxicities observed, particularly the highly significant signals for neutropenia and lymphopenia, are deeply rooted in the pharmacological mechanisms of Isa-Pd. Isatuximab depletes target cells primarily through antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) (Sakaeda T, et al. 2013; Sanchez L, et al. 2016). While CD38 is highly expressed on malignant plasma cells, it is also present on normal immune effectors (e.g., NK cells, B lymphocytes, and T cells), leading to profound lymphopenia (Dimopoulos M, et al. 2025; Frerichs KA, et al. 2018). Furthermore, the myelosuppressive effects are synergistically exacerbated by the concomitant use of pomalidomide and dexamethasone, both of which possess intrinsic myelosuppressive properties (Sanchez L, et al. 2016).

Marked differences were observed between Lecheng and FR cohort. The Lecheng group had a higher proportion of males and elderly patients, all AEs were reported by physicians and lead to hospitalisation, TTO occurred earlier. FR group showed a broader outcome spectrum and a more dispersed time distributions. Comparing the PT and SOC levels, AE signals in the Lecheng group were highly concentrated on laboratory test abnormalities (especially Neutrophil count decreased with an extremely high signal intensity), whereas the FR group presented clinical events such as Hypertension and COVID-19 infection, involving Vascular disorders and Infections. can be primarily attributed to distinct healthcare management models. The Lecheng cohort operates under a comprehensive full-cycle patient management system—encompassing pre-treatment risk assessment, prophylactic interventions, intensive monitoring, and post-treatment care. This rigorous supervision results in highly proactive monitoring and 100% physician-driven reporting, capturing even mild laboratory fluctuations and artificially inflating the ROR. In contrast, the FAERS data use spontaneous reporting systems to update, which are inherently limited by under-reporting and reporting biases.

Beyond these known toxicities, we uncovered several unexpected AE signals compared with the medication instructions, including Pyrexia, Pancytopenia, Hypertension, Cardiac failure, Hypokalaemia, and opportunistic infections like Pneumocystis jirovecii pneumonia. These potential risks may arise from the cumulative toxicity of the regimen or the deep immunosuppression caused by the disease and CD38-targeted therapy (Portuguese AJ, et al. 2026; Rago A, et al. 2025). Therefore, manufacturers and clinicians must pay close attention to infection monitoring, strengthen the management of hematological toxicities, and add routine monitoring for cardiovascular events and metabolic disturbances.

To manage severe hematological toxicities, clinicians in the Lecheng cohort employed proactive supportive care strategies. Prophylactic administration of cytokines (e.g., G-CSF) is recommended for patients at risk of bone marrow suppression. Furthermore, certain traditional Chinese medicines (TCM)—such as Qijiao Shengbai Capsule, Diyu Shengbai Tablet, and Shengxuebao Mixture—may

serve as potential adjunctive options to standard cytokine therapies (Liu SS, et al. 2024; Peng BW, et al. 2026; Zhu L, et al. 2025; Cao Rui. 2012). However, further trials are needed to validate their specific pharmacological interactions with Isa-Pd. For infection management, strict adherence to pre-infusion prophylactic medications and timely administration of anti-infective therapies are essential.

Conclusion

By integrating the FAERS database with the Lecheng prospective real-world cohort, this study provides an externally validated safety landscape for Isa-Pd in RRMM. Beyond confirming conventional hematological toxicities, our analysis identified several unexpected risk signals—including cardiovascular events, metabolic disturbances, and severe opportunistic infections. Furthermore, the significant regional disparities between Lecheng and France underscore the impact of distinct healthcare models, specifically proactive full-cycle patient management versus spontaneous reporting. These findings provide robust pharmacological evidence for updating post-marketing safety profiles and implementing individualized risk mitigation strategies for patients receiving Isa-Pd.

Supplementary information The online version contains supplementary material available at XX

Acknowledgement We appreciated the Isatuximab Real-world study team in *RUIJIN-HAINAN* Hospital Shanghai Jiao Tong University School of Medicine Hainan Boao Research Hospital and Sanofi for attention on adverse event. We also acknowledge assistance from medical writers, proofreaders and editors.

Author contribution Q.C. was responsible for conceptualization, data curation, formal analysis, investigation, methodology, visualization, and wrote the initial draft of the manuscript. L.Z. was responsible for conceptualization and project administration. J.Y. contributed to data supervision and validation. L.Z. and J. Y. both provided expert guidance, and reviewed the final manuscript. Z.H. and X.C. contributed to investigation and validation. All authors reviewed and approved the final manuscript. The authors declare that all data were generated in-house, that no paper mill was used and that no AI tool has been used for the generation of text or figures.

Funding This study was supported by Hainan Provincial Pharmacovigilance Innovation Research Project of China in 2024 (HNPV202403).

Data availability FAERS data are available at http://www.fda.gov/. The dataset generated during and analyzed during the current study are available from the corresponding author on reasonable

request. Correspondence and requests for materials should be addressed to Q.C., or L.Z.

Declarations

Ethics declarations Ethical approval of FAERS data was not required as the study was conducted using deidentified publicly available data. Lecheng data ethical approval for the study was approved by the Ethics Committee of Shanghai Jiaotong University School of Medicine, Ruijin-Hainan Hospital (No. 20250113).

Competing interests The authors declare no competing interests.

References

An G, Jin J, Cai Z, et al (2025) Talquetamab, a GPRC5D×CD3 bispecific antibody, in Chinese patients with relapsed/refractory multiple myeloma: efficacy and safety from the phase 1/2 MonumenTAL-1 study. Haematologica 111:1411–1416. https://doi.org/10.3324/haematol.2025.287334

Bate A, Lindquist M, Edwards IR, et al (1998) A Bayesian neural network method for adverse drug reaction signal generation. European Journal of Clinical Pharmacology 54:315–321. https://doi.org/10.1007/s002280050466

Boissel N, Chevallier P, Doronin V, et al (2022) Isatuximab monotherapy in patients with refractory T-acute lymphoblastic leukemia or T-lymphoblastic lymphoma: Phase 2 study. Cancer Medicine 11:1292–1298. https://doi.org/10.1002/cam4.4478

Chen W, You J, Lin L, et al (2025) Real-world outcomes of isatuximab with pomalidomide and dexamethasone for relapsed and/or refractory multiple myeloma. Chinese Medical Journal 139:589–596. https://doi.org/10.1097/cm9.0000000000003649

Chen Y, Tao S, Zheng X, et al (2021) Research progress on treatment of extramedullary multiple myeloma. Hematology 26:985–994. https://doi.org/10.1080/16078454.2021.2005310

Coffman K, Carstens C, Fajardo S (2022) Daratumumab infusion reaction rates pre- and post-addition of montelukast to pre-medications. Journal of Oncology Pharmacy Practice 29:333–337. https://doi.org/10.1177/10781552211072876

Dhillon S (2020) Isatuximab: First Approval. Drugs 80:905–912. https://doi.org/10.1007/s40265-020-01311-1

Dimopoulos M, Sunami K, Leleu X, et al (2025) Efficacy and safety of isatuximab monotherapy to treat relapsed or refractory multiple myeloma: a pooled analysis of clinical trials. Annals of Hematology 104:2337–2350. https://doi.org/10.1007/s00277-025-06343-9

Dou X, Duan G, Zhong Y, et al (2025) The burden of multiple myeloma in China: Trends from 1990 to 2021 and forecasts for 2050. Cancer Letters 611:217440. https://doi.org/10.1016/j.canlet.2025.217440

Encinas C, Blanchard MJ, Fernández RA, et al (2025) Factors Increasing the Risk of Infection in Patients With Multiple Myeloma: From Biology to Prevention. Clinical Lymphoma Myeloma and Leukemia 25:e844-e856.e1. https://doi.org/10.1016/j.clml.2025.06.012

Fedyk ER, Zhao L, Koch A, et al (2020) Safety, tolerability, pharmacokinetics and pharmacodynamics of the anti-CD38 cytolytic antibody TAK-079 in healthy subjects. British Journal of Clinical Pharmacology 86:1314–1325. https://doi.org/10.1111/bcp.14241

Frerichs KA, Nagy NA, Lindenbergh PL, et al (2018) CD38-targeting antibodies in multiple myeloma: mechanisms of action and clinical experience. Expert Review of Clinical Immunology 14:197–206. https://doi.org/10.1080/1744666x.2018.1443809

Tan CR, Asoori S, Huang C-Y, et al (2025) Real-world evaluation of teclistamab for the treatment of

relapsed/refractory multiple myeloma (RRMM): an International Myeloma Working Group Study. Blood Cancer Journal 15:. https://doi.org/10.1038/s41408-025-01259-z

van de Donk NWCJ, Richardson PG, Malavasi F (2018) CD38 antibodies in multiple myeloma: back to the future. Blood 131:13–29. https://doi.org/10.1182/blood-2017-06-740944

van Puijenbroek EP, Bate A, Leufkens HGM, et al (2002) A comparison of measures of disproportionality for signal detection in spontaneous reporting systems for adverse drug reactions. Pharmacoepidemiology and Drug Safety 11:3–10. https://doi.org/10.1002/pds.668

Vassilopoulos S, Vassilopoulos A, Kalligeros M, et al (2022) Cumulative Incidence and Relative Risk of Infection in Patients With Multiple Myeloma Treated With Anti-CD38 Monoclonal Antibody-Based Regimens: A Systematic Review and Meta-analysis. Open Forum Infectious Diseases 9:. https://doi.org/10.1093/ofid/ofac574

Sakaeda T, Tamon A, Kadoyama K, Okuno Y (2013) Data Mining of the Public Version of the FDA Adverse Event Reporting System. International Journal of Medical Sciences 10:796–803. https://doi.org/10.7150/ijms.6048

Sanchez L, Wang Y, Siegel DS, Wang ML (2016) Daratumumab: a first-in-class CD38 monoclonal antibody for the treatment of multiple myeloma. Journal of Hematology & Oncology 9:. https://doi.org/10.1186/s13045-016-0283-0

Portuguese AJ, Davis JA, Raza S, et al (2026) Real-world outcomes with elranatamab in multiple myeloma: a multicenter analysis from the U.S. Multiple Myeloma Immunotherapy Consortium. Blood Cancer Journal 16:. https://doi.org/10.1038/s41408-026-01477-z

Rago A, Fioritoni F, Liberatore C, et al (2025) Infection events in patients with newly diagnosed multiple myeloma with anti-CD38 monoclonal antibody-based first line regimens: A multicentric Italian experience. Annals of Hematology 104:5323–5331. https://doi.org/10.1007/s00277-025-06645-y

Liu SS, Wang AJ, Sun XD, et al (2024) Clinical efficacy of Qijiao Shengbai capsules in the prevention and treatment of malignant tumors with myelosuppression after chemoradiotherapy: a meta-analysis. China Pharmaceuticals 33:121–128.https://shrj.lib4s.com/s/net/cnki/kns/G.https/kcms2/article/abstract?v=TEFJyEEsApG1wR0lvhOp1ixIbrV8zlFV8Ltv5zAcN5hEbFKwzdqY3dDIXMM1HNSH4XcNgj0y4rUon8zyBUXkoKs52bxvNL7S8Kya-h1ZHYYtmlx18MmhEgKvP6C98OEaIMrk5EOs5WfN5GbW607yeG8dP4RQHNXcyUTivVL5lpKKZPSDYkCptQ==

Peng BW, Wu J, Chen XY, et al (2026) Clinical comprehensive evaluation of Diyu Shengbai tablets in the treatment of leukopenia. Beijing Journal of Traditional Chinese Medicine 45:30–41. https://doi.org/10.16025/j.1674-1307.2026.01.007

Zhu L, Xiangrong L, Xiaojun D, et al (2025) A randomized, double-blind, placebo-controlled, multicenter clinical study of Shengxuebao Mixture in treating cancer-related anemia. Journal of Beijing University of traditional Chinese Medicine 48:1447–1459. https://doi.org/10.3969/j.issn.1006-2157.2025.10.015

Cao Rui. (2012) The Study on Effective Substance and Evaluation of Quality of WXN. Dissertation, Shanxi University of Chinese Medicine.

Table Caption

Table 1. Methods, formulas, and thresholds for Reporting Odds Ratio (ROR), Proportional Reporting Ratio (PRR), Bayesian Confidence Propagation Neural

Network (BCPNN), and Muti-item Gamma Poisson Shrinker (MGPS). (a) Count of reports featuring both the specified drug and target adverse events; (b) number of reports involving other adverse drug events alongside the specified drug; (c) reports of target adverse drug events involving other drugs; (d) reports encompassing other drugs and non-targeted adverse drug events.

95% CI: 95% confidence interval; N: number of reports; χ2: chi-squared; IC: information component; IC025: lower limit of 95% CI of the IC; E (IC): IC expectations; V(IC): variance of IC; EBGM05: lower limit of 95% CI of EBGM.

Table 2. Characteristics of reports in Lecheng and France associated with Isa-Pd from 2020 Q1 to 2025 Q4.

Table 3. Signal strength of Serious adverse reports of Isa-Pd at the SOC level in FAERS and Lecheng database.

*Indicates statistically significant signals in algorithm. SOC, system organ class; ROR, reporting odds ratio; CI, confidence interval; PRR, proportional reporting ratio; χ^2, chi-information component; IC, information component; IC025, the lower limit of 95% CI ofthe IC; EBGM, empirical Bayesian geometric mean; EBGM05, the lower limit of 95% CI of EBGM; -, the range of the 95% confidence interval.

Table 4. Signal strength of reports of Isa-Pd at the SOC level between Lecheng and FR.（*P*-value <0.0001）

*Indicates statistically significant signals in algorithm. 95% CI = 95% confidence interval, EBGM = empirical bayes geometric mean, EBGM05 = the lower limit of 95% CI of EBGM, IC = information component, IC025 = the lower limit of 95% CI of the IC, PRR = proportional reporting ratio, ROR = the reporting odds ratio, χ2 = chi-squared; -, the range of the 95% confidence interval.

Table 5. Signal strength of reports of Isa-Pd at the PT level between Lecheng and FR.（*P*-value <0.0001）

*Indicates statistically significant signals in algorithm. 95% CI = 95% confidence interval, EBGM = empirical bayes geometric mean, EBGM05 = the lower limit of 95% CI of EBGM, IC = information component, IC025 = the lower limit of 95% CI of the IC, PRR = proportional reporting ratio, ROR = the reporting odds ratio, SOC = system organ class, χ2 = chi-squared; -, the range of the 95% confidence interval.

Figure Legends

Fig. 1. Data collected consists FAERS and LeCheng: 1. From 2020Q1 to 2025Q4, 10,355898 FAERS DEMO have been download, after duplication and China records(n=1,622,280), get FAERS unique DEMO (n=8,733,618). 2. From 2022Q3 to 2024Q2, 91 LeCheng DEMO has been collect, After duplication records (n=3), get unique LeCheng DEMO (n=88). Involving these two parts and setting combined medication regimen as “Isa-PD”("ISATUXIMAB" index 'POMALIDOMIDE' and 'DEXAMETHASONE'), then got Combined DEMO (n=7,071,990). DRUG data (n=24,109 619) was merged with Combined DEMO, corresponding to 507 reports. REAC data (n=187,702,264) was merged with Combined DEMO, corresponding to 1,119 AEs. Limited the reporter country as "China" and“France”, we finally got 200 reports (266 AEs).

Fig. 2. 95% CI = 95% confidence interval.

Fig. 3. (A)shows top 50 PTs by Frequency for adverse events and their belonging of SOC. (B)displays the results of disproportionality analysis by ROR, PRR, BCPNN and MGPS.

Fig. 4. (A) shows Fatal subgroup, (B) shows Serious subgroup.

Fig. 5. (A) presents the distribution of Top 50 PTs Across Different Non-/Serious adverse events by heatmap. (B) displays the results of disproportionality analysis by ROR, PRR, BCPNN and MGPS. IQR, interquartile range.

Fig. 6. The results of disproportionality analysis by ROR, PRR, BCPNN and MGPS. The X-axis represents the logarithm of the p-value based on Fisher's exact test (−log10P), and the Y-axis represents the negative logarithm of the ROR (log2ROR). Dots represent fatal factors.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- 2.Supportingimformation.docx