Journal for ImmunoTherapy of Cancer

Characteristics of second primary malignancies following bispecific antibodies therapy

Xiaojie Liang [1], Baiwei Luo [2], Bingyu Lin [2], Dan Liu [3], Jia Guo [1], Weixiang Lu [1], Shengyu Tian [1], Zihong Cai [2], Xinyu Zhou [4], Zhihao Jin [4], Tong Li [5], Keren Chen [6], Hongsheng Zhou [2], Liang Wang [1]

To cite: Liang X, Luo B, Lin B, *et al*. Characteristics of second primary malignancies following bispecific antibodies therapy. *Journal for ImmunoTherapy of Cancer* 2025;**13**:e011200. doi:10.1136/jitc-2024-011200

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/jitc-2024-011200).

XL, BL and BL contributed equally.

Accepted 24 March 2025

For numbered affiliations see end of article.

Correspondence to
Dr Liang Wang;
wangliangtrhos@126.com

Professor Hongsheng Zhou;
hanson_tcm@126.com

ABSTRACT

Background The risk of secondary primary malignancies (SPMs) associated with bispecific antibody (BsAb)—a promising alternative to chimeric antigen receptor (CAR)-T therapy—remains insufficiently explored.

Methods Using large-scale, real-world data from the US Food and Drug Administration's Adverse Event Reporting System, we identified the relative frequency and characteristics of SPMs following BsAbs therapy and conducted a comprehensive comparison of treatment-related SPM profiles between BsAbs and CAR-T therapies.

Results We identified 108 cases among 10,280 BsAb-treated patients. The incidence risk of SPMs was stable over the past 8 years, accounting for 1–2% of all adverse events, with a case fatality rate of 29.63% among the SPM cases. Myeloid leukemias and non-Hodgkin's lymphoma were more frequent in blinatumomab recipients, while solid malignancies predominated in those treated with teclistamab. Time-to-onset (TTO) was significantly shorter in BsAb recipients compared with non-recipients, with weight and treatment duration influencing TTO, while no significant differences in TTO were observed across different BsAb products, ages, and genders. Our findings highlight the first year of BsAbs as a critical window for early detection and intervention. Although the overall risk of SPMs was lower with BsAbs than with CAR-T, the outcomes of SPMs were comparable in both groups. TTO and SPM patterns were statistically similar between the two therapies.

Conclusion Our study provides the first detailed characterization of SPMs post-BsAb, underscoring the need for continued pharmacovigilance and individualized risk management to mitigate SPM risks in patients undergoing BsAb therapy.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Secondary primary malignancies (SPMs) following chimeric antigen receptor (CAR)-T therapy have garnered global attention; however, the risk of SPMs associated with bispecific antibody (BsAb)—a promising alternative to CAR-T with similar mechanisms of action and targets—remains insufficiently explored.

WHAT THIS STUDY ADDS

⇒ Our study provides the first comprehensive analysis of SPMs following BsAbs therapy using large-scale, real-world data from the Food and Drug Administration's Adverse Event Reporting System database, and performs a detailed comparison of SPM profiles between BsAbs and CAR-T therapies. Our findings reveal that BsAbs therapy is associated with a significant, yet relatively underappreciated, risk of SPMs, highlighting the urgent need for continued pharmacovigilance and individualized risk management to balance efficacy and safety in this emerging immunotherapy.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our findings are pivotal for oncologists, hematologists, and healthcare providers, as they provide the necessary insights to refine patient monitoring strategies and optimize therapeutic decisions in the clinical practice of BsAbs therapy. We appeal to ongoing clinical trials of BsAbs, as well as clinicians treating patients with BsAbs, to report any newly diagnosed cancers. Additionally, we recommend that patients receiving these therapies and participants in clinical trials undergo regular monitoring for new cancers.

INTRODUCTION

Chimeric antigen receptor (CAR) T cell therapies and bispecific antibodies (BsAbs) represent significant breakthroughs in clinical oncology. For example, long-term follow-up data reveal sustained disease-free survival in 30–40% of patients with B-cell subtypes of non-Hodgkin's lymphoma treated with CD19-targeted CAR-T (CAR-19) therapies.[1 2] BsAbs are engineered proteins designed to bind two distinct antigens or two different epitopes on the same antigen concurrently.[3] There are five main types of BsAbs based on their mechanisms: T-cell engagers (TCEs), bispecific immunomodulatory antibodies,

bispecific antibody-drug conjugates, bispecific receptor activators, and bispecific immune checkpoint inhibitors.[4] T-cell redirecting BsAbs bind to and activate effector T cells, directing them toward tumor-cell antigens, thereby inducing cytotoxicity similar to that of CAR-T therapies.[5] In 2023, BsAbs glofitamab and epcoritamab received initial approvals for use in diffuse large B-cell lymphoma as third-line or later therapies, or for patients unsuitable for CAR-19 treatment.[6] Furthermore, the introduction of CAR-T cell and T-cell redirecting BsAb therapies has resulted in remarkable response rates and sustained responses in relapsed/refractory multiple myeloma (RRMM). In the USA, two B-cell maturation antigen (BCMA)-directed CAR-T therapies (ciltacabtagene autoleucel and idecabtagene vicleucel) and one BCMA/CD3 BsAb (teclistamab) are currently approved for use in late-line (beyond four prior therapies) RRMM.[7] Since personalized CAR T cells typically require 6–8 weeks for manufacturing and intravenous infusion to patients, in contrast, BsAbs are readily available and do not require bridging therapy. This allows BsAb treatment to be extended to patients with rapidly progressing diseases.[5] By the end of 2023, 14 BsAbs had been approved: 11 for oncology and 3 for non-oncology indications.[4]

Despite the remarkable efficacy, recent reports of secondary primary malignancies (SPMs) following CAR-T therapy have garnered global attention. A recent study, including 724 CAR-T infused patients at Stanford University Medical Center from February 4, 2016 to January 15, 2024, identified 25 cases of secondary tumors after a median follow-up of 15 months.[8] Potential contributing factors include viral vector integration into the host genome, clonal hematopoietic mutations, overactivated T-cell and inflammatory signaling environment, and T-cell exhaustion.[8–12] On November 28, 2023, the US Food and Drug Administration (FDA) announced an investigation into potential secondary T-cell malignancies associated with CAR-T immunotherapy.[13] As an alternative therapeutic approach to CAR-T therapy, BsAbs therapy demonstrates similar efficacy and shares common adverse effects, including cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome, tumor lysis syndrome, and an increased risk of infections.[5 14] Notably, in addition to immune hyperactivation, BsAbs can also lead to T-cell exhaustion and chronic inflammation.[15 16] However, whether BsAbs also contribute to SPMs remains an unmet clinical issue.

In this study, to evaluate the potential risks of SPMs following BsAbs therapy, we used large-scale, real-world data from the global pharmacovigilance database to thoroughly investigate the characteristics and determinants of SPMs associated with BsAbs therapy. These efforts will inform future safety monitoring protocols for BsAb products.

METHODS

Data source

Leveraging the FDA Adverse Event Reporting System (FAERS) publicly available database, we investigated the frequency and association of SPMs reporting with BsAbs and the prognostic implications of SPMs in patients receiving BsAbs. FAERS is a publicly available database of drug safety reports submitted by patients, healthcare professionals, and pharmaceutical companies. It is partitioned into four quarters annually. In our study, we used data from the last quarter of 2014 (the first approval of a BsAbs product, blinatumomab) to the first quarter of 2024 (the latest available date). Thus, our analysis included adverse event (AE) reports from October 2014 to March 2024.

Data processing procedure

We deduplicated all reports obtained from FAERS. When multiple reports of the same case were detected, only the latest report version of each event was retained, as recommended by the FDA.[17] The terminology of drug indications and adverse reactions in FAERS was compared and matched with the preferred term from the Medical Dictionary for Regulatory Activities V.27.0 (MedDRA V.27.0). The four types of BsAb products under consideration were anti-CD19-CD3 (blinatumomab), anti-CD20-CD3 (mosunetuzumab, glofitamab, epcoritamab), anti-BCMA-CD3 (teclistamab, elranatamab), and other (amivantamab, tebentafusp, talquetamab). These nine products are currently the BsAbs approved by the FDA specifically for cancer therapy. For the analysis of SPMs after BsAbs treatment, we only considered cases where BsAbs were identified as the "primary suspect (PS)" drug in FAERS. According to the definition of SPMs, we extracted cases with malignancies using the MedDRA tumor-related Standardised MedDRA Query (SMQ) codes (malignancies, uterine and fallopian tube neoplasms, malignant and unspecified, skin neoplasms, malignant and unspecified, ovarian neoplasms, malignant and unspecified, prostate neoplasms, malignant and unspecified, myelodysplastic syndrome, malignant lymphomas) and identified SPM cases based on tumor-related SMQ codes, excluding relevant inspection, examination, and treatment codes (tumor markers, malignancy-related therapeutic and diagnostic procedures, and malignancy-related conditions). The cases list with SPMs can be seen in the online supplemental table S1.

Pharmacovigilance analysis

Disproportionality analysis is a statistical approach used for detecting potential adverse drug reaction signals from large databases. This method helps identify safety signals, which are unexpected or previously unknown potential risks associated with a drug. These signals suggest that the drug is associated with specific AEs more frequently than other drugs in the database. Moreover, disproportionality analysis quantifies the association between a drug and an AE using various statistical measures, including the

proportional reporting ratio (PRR), reporting OR (ROR), and the Bayesian confidence propagation neural network (BCPNN) information component.[18–21] In this study, we used the ROR, PRR, and BCPNN methods to examine the association between SPMs and BsAbs. We created a drug adverse reaction contingency table (as detailed in the online supplemental methods) and referred to it as the basis for subsequent signal analysis. In this table, a represents the number of cases that developed SPMs post BsAbs therapy; b represents the number of cases that experienced other non-SPM AEs in BsAbs recipients; c represents the number of cases that developed SPMs without BsAbs therapy; d represents the number of cases that experienced other non-SPM AEs without BsAbs therapy.

A positive signal is defined as the number of cases of an AE no less than three and the lower limit of the 95% CI of the ROR/PRR exceeding one as described previously. For the BCPNN analysis, a positive signal is defined as the number of an AE no less than three and the lower limit of the 95% CI exceeding one. In this study, if the assessed SPM meets these criteria as a positive signal for FAERS, it will be graded as a potentially high-risk SPM after BsAbs therapy.[22] We also compared the differences in the drug-event risk signal between BsAbs and CAR-T therapies.

Time-to-onset analysis

In FAERS, time-to-onset (TTO) is defined as the interval between EVENT_DT (the date of occurrence of AEs) and START_DT (the date when drugs start to be used). Using FAERS data, we employed cumulative distribution curves to illustrate the TTO of SPMs in patients treated with and without BsAbs, and to compare the TTO of SPMs across subgroups based on gender, age, BsAb products, body weight, and treatment duration among patients who developed SPMs after BsAb therapy. We also compared the onset time of SPMs between recipients of BsAbs and CAR-T therapies.

Statistical analysis

Descriptive data are reported as numbers (percentages), medians (IQR), and means (SD). To assess the severity of outcomes among patients experiencing a specific AE, we calculated the case fatality rate (CFR), defined as the proportion of fatal outcomes among reported cases of specific toxicities. To compare the baseline characteristics between CAR-T recipients and non-recipients, categorical and numerical variables were analyzed using the χ^2 test and Mann-Whitney U test, respectively. The Mann-Whitney U test and Kruskal-Wallis test were used to compare the differences in median time to SPM onset between CAR-T and non-CAR-T cases in further stratified analyses regarding different sexes, age clusters, and cancer subtypes. All analyses were performed using R (V.4.4.1). A two-sided p value less than 0.05 is considered as statistical significance.

RESULTS

Comprehensive overview of common AEs and SPMs post BsAbs therapy

The detailed data processing workflow of this study is shown in figure 1. Of the 13,014,472 patient entries in the FAERS database from October 2014 to March 2024, 108 SPMs were reported in 10,280 cases related to BsAbs (figure 1). The most frequently reported AEs were CRS, fever, and recurrent acute lymphocytic leukemias, with

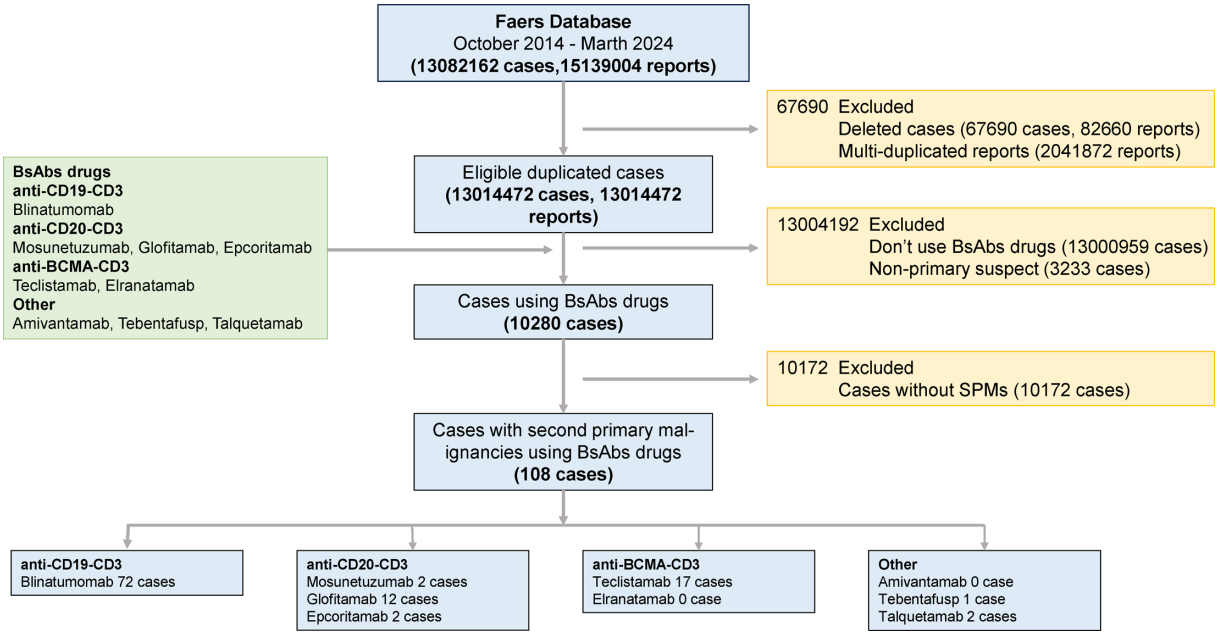

Figure 1 Study flow diagram for included cases identified from quarterly files in the FAERS from the last quarter of 2014 to the first quarter of 2024. BCMA, B-cell maturation antigen; BsAbs, bispecific antibodies; FAERS, Food and Drug Administration's Adverse Event Reporting System; SPM, secondary primary malignancy.

death cases of 260 (20.87%), 149 (14.48%), and 209 (34.83%), respectively.

While SPMs accounted for a minor proportion of all AEs following BsAbs therapy, their CFR was notably high at 29.63%, placing them among the top 10 most fatal common adverse reactions, excluding death (figure 2A). The cases of SPMs remained relatively stable over the past 8 years, exceeding or near 1% in all BsAbs AEs. Remarkably, the frequency of hematological malignancies declined over time, whereas solid tumors showed an increasing trend (figure 2B). Myeloid leukemias were the most common SPMs among hematological malignancies, and gastrointestinal neoplasms, respiratory tract cancers, renal and urinary tract neoplasms and hepatobiliary neoplasms were the common among solid malignancies (figure 2C). Additionally, distinct bispecific products were linked to specific types of SPMs. For example, myeloid leukemias and non-Hodgkin's lymphoma were most often observed following blinatumomab therapy, whereas solid malignancies were more commonly associated with teclistamab treatment (figure 2C). Moreover, we used the Sankey diagram to examine the evolutionary trajectory between first primary malignancies (FPMs) and SPMs following BsAbs. The diagram revealed that plasma cell myeloma, B-cell lymphoma and follicular lymphoma were predominantly associated with subsequent solid malignancies, whereas acute lymphocytic leukemia was more frequently followed by hematological malignancies post-BsAb treatment (figure 2D).

Characteristics in BsAb-treated versus untreated patients and post-BsAb with versus without SPMs

In comparing the clinical characteristics of patients who did or did not receive BsAbs treatment, we found significant statistical differences in terms of gender, age groups, weight, and geographic location (p<0.001) (online supplemental table S2). Among patients receiving BsAbs treatment, males were more commonly represented (53% vs 47%). Notably, we observed that the proportion of elderly patients receiving BsAbs treatment was significantly lower compared with those not receiving BsAbs treatment (26% vs 35%), which may be related to the poorer tolerance of antitumor therapies in the elderly population.

We also compared the demographic and clinical features of patients with and without SPMs post BsAbs therapy (table 1). Significant differences were observed in age and reporting continents (p<0.001), whereas no substantial differences were found in gender or weight. In the FAERS database, SPM reports predominantly originate from Europe and the Americas. Interestingly, we found that nearly half of the SPM cases involved elderly patients, which is significantly higher compared with patients without SPMs (42% vs 26%). This suggests that SPMs post-BsAbs therapy appear to be more prevalent among the elderly population.

Pharmacovigilance signals for the SPMs post BsAbs therapy

To further identify potential SPMs that could represent significant safety signals following BsAbs therapy, we conducted disproportionality analysis in patients who received BsAbs. The results from the three signal detection methods (ROR, PRR, BCPNN) were largely consistent, indicating a preferential association of specific malignancies as SPMs after BsAbs therapy (figure 3A–C). Myelodysplastic syndromes (ROR: 55.05 (28.23, 107.32), PRR: 55.00 (28.21, 107.23), $BCPNN_{IC025}$: 1.91), myeloid leukemias (ROR: 12.86 (9.52, 17.38), PRR: 12.81 (9.48, 17.31), $BCPNN_{IC025}$: 2.09), non-Hodgkin's lymphoma (ROR: 7.68 (4.35, 13.55), PRR: 7.67 (4.35, 13.54), $BCPNN_{IC025}$: 1.16), soft tissue neoplasms (ROR: 7.25 (2.71, 19.38), PRR: 7.25 (2.71, 19.37), $BCPNN_{IC025}$: 0.21), gastrointestinal neoplasms (ROR: 2.86 (1.49, 5.51), PRR: 2.86 (1.49, 5.50), $BCPNN_{IC025}$: 0.18), hepatobiliary neoplasms (ROR: 4.05 (1.68, 9.75), PRR: 4.05 (1.68, 9.74), $BCPNN_{IC025}$: 0.08) and respiratory tract cancers (ROR: 3.92 (1.63, 9.43), PRR: 3.92 (1.63, 9.42), $BCPNN_{IC025}$: 0.08) have been the positive safety signals post BsAbs therapy.

To further investigate the association between BsAbs and the occurrence of SPMs, and to adjust for the influence of other factors (such as survivorship bias), we performed logistic regression analysis, adjusting for multiple covariates including age, sex, weight, and region (online supplemental table S3). The univariate logistic regression analysis revealed that patients receiving BsAbs therapy had an OR of 4.19 for developing SPMs compared with those not receiving BsAbs therapy (95% CI: 2.94 to 5.99, p<0.001). Furthermore, the multivariate logistic regression analysis confirmed that, after adjusting for the aforementioned covariates, BsAbs therapy remained a significant risk factor for SPMs (OR 3.96, 95% CI: 2.77 to 5.66, p<0.001).

We further examined the association between different types of BsAb products and the occurrence of specific SPMs. Myelodysplastic syndromes (ROR: 58.11 (25.80, 130.87), PRR: 58.05 (25.78, 130.75)), myeloid leukemias (ROR: 19.25 (14.08, 26.30), PRR: 19.13 (14.00, 26.15)), non-Hodgkin's lymphoma (ROR: 8.21 (4.10, 16.45), PRR: 8.20 (4.09, 16.43)) and hepatobiliary neoplasms (ROR: 3.90 (1.26, 12.11), PRR: 3.90 (1.26, 12.10)) emerged as the major SPMs post CD19-CD3 BsAbs therapy, while the incidence risk of gastrointestinal neoplasms (ROR: 15.31 (6.36, 36.88), PRR: 15.25 (6.33, 36.72)) was higher in patients receiving CD20-CD3 BsAbs therapy. For BCMA-CD3 bispecific products, soft tissue neoplasms (ROR: 25.53 (6.37, 102.40), PRR: 25.50 (6.36, 102.26)), renal and urinary tract neoplasms (ROR: 8.85 (2.21, 35.45), PRR: 8.84 (2.20, 35.41)), respiratory tract cancers (ROR: 11.05 (2.76, 44.25), PRR: 11.03 (2.75, 44.19)), hepatobiliary neoplasms (ROR: 11.42 (2.85, 45.75), PRR: 11.41 (2.85, 45.69)), and non-Hodgkin's lymphoma (ROR: 8.99 (2.24, 36.01), PRR: 8.98 (2.24, 35.96)) were the major SPMs. For other BsAbs types (including EGFR-MET, gp100-HLA-CD3, GPRC5D-CD3), non-Hodgkin's lymphoma and myeloid leukemias were also identified,

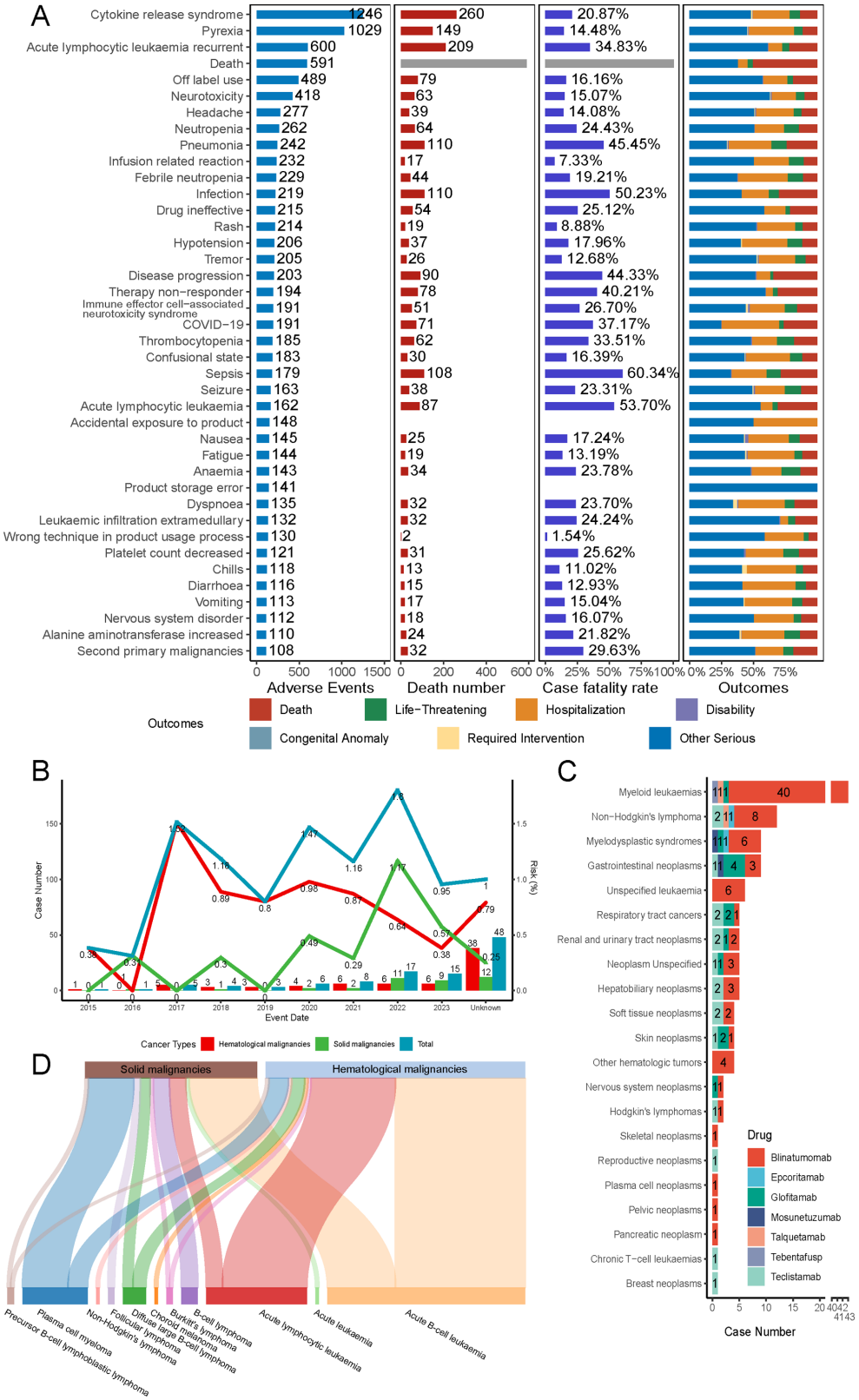

Figure 2 The overview of common adverse events and SPMs post BsAbs therapy. (A) The cases number, death number, case fatality rate and outcomes of the common adverse events post BsAbs therapy. (B) The histogram illustrates the annual case counts of SPMs (including hematological malignancies and solid malignancies) post BsAbs therapy. The line diagram depicts the annual incidence risk, which was calculated by dividing the number of reported SPM cases associated with BsAbs therapy each year by the total number of adverse event cases related to BsAbs treatment within the same year. (C) The bar chart counted the number of different SPMs, and different colors indicated different BsAb products. (D) The Sankey diagram shows the association between FPMs and SPMs. BsAbs, bispecific antibodies; FPMs, first primary malignancies; SPMs, secondary primary malignancies.

Table 1 Demographic and clinical characteristics of patients with and without SPMs post BsAbs therapy

Characteristic	Non-SPM n=10,172*	SPM n=108*	P value†
Gender			0.2
Female	3,557 (47)	36 (40)	
Male	3,991 (53)	55 (60)	
Unknown	2,624	17	
Age group			<0.001
Neonate	2 (<0.1)	0 (0)	
Infant	84 (1.5)	8 (11)	
Child	501 (9.1)	6 (8.1)	
Adolescent	290 (5.3)	1 (1.4)	
Adult	3,183 (58)	28 (38)	
Elderly	1,436 (26)	31 (42)	
Unknown	4676	34	
Weight			0.4
≤60 kg	862 (33)	12 (27)	
>60 kg	1,745 (67)	32 (73)	
Unknown	7,565	64	
Continents			<0.001
Africa	25 (0.3)	0 (0)	
Americas	5,829 (62)	36 (38)	
Asia	1,714 (18)	27 (29)	
Europe	1,674 (18)	29 (31)	
Oceania	168 (1.8)	2 (2.1)	
Unknown	762	14	

*n (%).
†Pearson's χ^2 test; Fisher's exact test.
BsAbs, bispecific antibodies; SPMs, secondary primary malignancies.

although these findings did not reach statistical significance (figure 3D–E; Online supplemental figure S1A-B).

TTO analysis of SPMs

To further investigate whether BsAbs contribute to the development of SPMs, we conducted the TTO analysis. In general, SPMs tended to occur sooner following BsAbs therapy compared with non-BsAbs (median TTO: 124 (78, 225) days versus 424 (402, 448) days; p<0.0001) (figure 3F). We conducted additional analyses to identify factors potentially influencing TTO in BsAbs recipients, including gender, age, BsAb types, weight, and duration of treatment. No statistically significant differences were found in various genders (figure 3G), ages (figure 3H), or BsAb groups (figure 3I). In contrast, both patient weight and treatment duration significantly impacted TTO in those receiving BsAbs. Patients weighing<60 kg had a shorter median TTO than those weighing>60 kg (median TTO: 12 (1, NA) days versus 236 (176, 451) days; p=0.0019) (figure 3J). Furthermore, a delayed occurrence trend of SPMs was observed in patients with a longer treatment duration (>3 months) compared with those with a shorter treatment duration (<3 months) (median TTO: 413 (251, NA) days versus 101 (13, 607) days; p=0.0187) (figure 3K). Insightfully, there are 38% recipients who would develop SPMs within 3 months, and 80% recipients would develop SPMs within the first year (online supplemental figures S1C).

Differences in SPMs between BsAbs and CAR-T therapies

We conducted a comparative analysis of SPMs between BsAbs and CAR-T therapies. No significant differences were observed in gender and weight among patients with SPMs receiving BsAbs and CAR-T treatment (table 2). For CAR-T therapy, the majority of SPM reports predominantly originated from the Americas (73%). The proportion of SPMs following BsAbs treatment is higher in young patients (including infants, children, and adolescents) compared with those receiving CAR-T therapy (20.5% vs 0.9%). These findings suggest that heightened vigilance is warranted for the risk of SPMs in patients receiving BsAbs, irrespective of age groups. Furthermore, SPMs constitute approximately 1.05% of all AEs related to BsAbs, compared with 3.05% for CAR-T therapy (figure 4A). Regarding outcomes for patients with SPMs, the CFR was 29.63% in BsAbs therapy, compared with 33.62% in the CAR-T group. Severe life-threatening conditions and hospitalizations were reported in 12.04% and 34.26% of patients with SPMs in the BsAbs group, respectively, while the corresponding percentages in the CAR-T group were 8.41% and 19.42% (figure 4B). Both the ROR and PRR for SPMs were higher with CAR-T therapy than with BsAbs, suggesting a potentially greater risk of SPMs associated with CAR-T therapy (figure 4C). While similar patterns of SPMs were observed in both BsAbs and CAR-T therapies, the risk of nervous system neoplasms (ROR: 6.25 (3.12, 12.52), PRR: 6.25 (3.12, 12.51)), skin neoplasms (ROR: 17.19 (13.71, 21.54), PRR: 17.08 (13.63, 21.40)), breast neoplasms (ROR: 5.68 (2.83, 11.38), PRR: 5.67 (2.83, 11.37)), and reproductive neoplasms (ROR: 10.60 (6.74, 16.66), PRR: 10.58 (6.73, 16.63)) was notably higher in the CAR-T therapy group (figure 4D; Online supplemental figure S1D). Notably, although the proportion of SPMs among AEs was higher with CAR-T therapy compared with BsAbs, the time to onset of SPMs did not significantly differ between the two therapies, regardless of whether all products or only those targeting CD19 and BCMA were considered (figure 4E–G).

Comparative analysis of SPMs across different cancer types and treatment modalities

We also compared the risk of SPMs following BsAbs therapy across different cancer types characterized by distinct disease biology, prior treatments, and potential genetic risks. The results showed that the risk of SPMs is 1.01% for acute lymphoblastic leukemia (ALL), 1.61% for lymphoma, 1.55% for myeloma, and 0.29% for solid malignancies (online supplemental figure S2A).

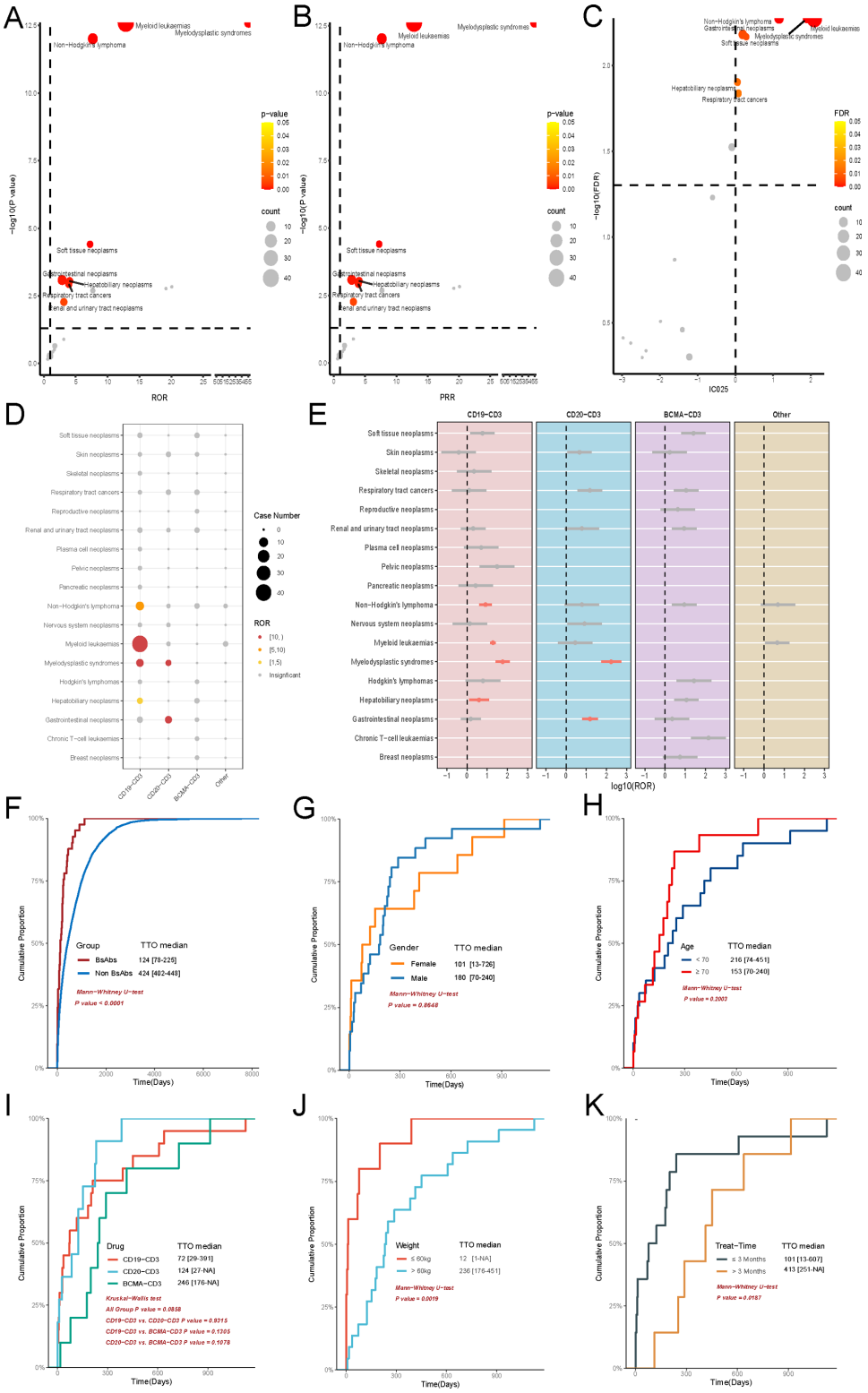

Figure 3 Identification of high-risk SPMs post BsAbs therapy and time-to-onset analysis of SPMs. (A, B and C) The bubble plot shows ROR (A), PRR (B), and BCPNN (C) values of all SPMs following BsAbs treatment, and the gray bubble does not meet the positive signal condition. (D and E) Signal comparison between CD19-CD3, CD20-CD3, BCMA-CD3 and other BsAbs. Dot plot presenting ROR values and cases number of SPMs (D). Forest plot presenting ROR values of SPMs with significant signals across all targets in FAERS. The error bars show the 95% CI of the ROR. Red signifies a significant positive signal, whereas gray denotes insignificance (E). (F–K) The cumulative distribution curve described the onset time of SPMs in BsAb-treated versus untreated patients (F), and in different groups stratified by gender (G), age (H), therapeutic target (I), weight (J), and treatment duration (K). BCMA, B-cell maturation antigen; BCPNN, Bayesian confidence propagation neural network; BsAbs, bispecific antibodies; FAERS, Food and Drug Administration's Adverse Event Reporting System; FDR, false discovery rate; PRR, proportional reporting ratio; ROR, reporting OR; SPMs, secondary primary malignancies; TTO, time-to-onset.

Table 2 Demographic and clinical characteristics of individuals with SPMs post BsAbs therapy and CAR-T therapy

Characteristic	BsAbs n=108*	CAR-T n=345*	P value†
Gender			0.089
Female	36 (40)	97 (30)	
Male	55 (60)	225 (70)	
Unknown	17	23	
Age group			<0.001
Infant	8 (11)	0 (0)	
Child	6 (8.1)	0 (0)	
Adolescent	1 (1.4)	2 (0.9)	
Adult	28 (38)	110 (49)	
Elderly	31 (42)	113 (50)	
Unknown	34	120	
Weight			0.7
≤60 kg	12 (27)	20 (24)	
>60 kg	32 (73)	64 (76)	
Unknown	64	261	
Continents			<0.001
Americas	36 (38)	250 (73)	
Asia	27 (29)	13 (3.8)	
Europe	29 (31)	71 (21)	
Oceania	2 (2.1)	8 (2.3)	
Unknown	14	3	

*n (%).
†Pearson's χ^2 test; Fisher's exact test.
BsAbs, bispecific antibodies; CAR, chimeric antigen receptor; SPMs, secondary primary malignancies.

Furthermore, we use two metrics—death proportion and CFR—to approximate and compare the mortality risks of SPMs associated with BsAbs versus those associated with three other therapies—CAR-T,[23] acalabrutinib,[24] and lenalidomide.[25] Additionally, we compared the risk of SPMs associated with the four therapies. Our analysis indicates that the risk of SPMs associated with BsAb therapy (1.05%) is comparable to that of acalabrutinib, a known BTK inhibitor associated with SPMs, but lower than that of CAR-T therapy and lenalidomide. The death proportion for SPMs following BsAbs therapy is 0.31%, which is lower than that observed in CAR-T therapy (1.03%) and lenalidomide (1.13%), but is higher than that in acalabrutinib (0.15%). When examining the CFR, the rate for BsAbs is 29.63%, which is modestly lower than that for CAR-T at 33.62%, yet higher than the CFR for acalabrutinib (12.90%) and lenalidomide (20.51%) (online supplemental figureS2B). These findings suggest that, although the risk of SPMs in patients receiving BsAb therapy is lower, the serious outcomes associated with these SPMs cannot be overlooked.

DISCUSSION

SPMs following CAR-T therapy have garnered global attention; however, the risk of SPMs associated with BsAb—a promising alternative to CAR-T with similar mechanisms of action and targets—remains underexplored. To address this gap, we conducted the first comprehensive analysis of SPMs following BsAbs therapy using large-scale, real-world data from the FAERS database, and performed a detailed comparison of SPM profiles between BsAbs and CAR-T treatments. Our study reveals that BsAbs therapy is associated with a significant, yet relatively underappreciated, risk of SPMs, highlighting a critical concern for this emerging immunotherapy.

By the end of 2023, over 300 clinical trials involving more than 200 different BsAb products were underway, with approximately 75% targeting solid tumors and 25% focusing on hematologic malignancies.[4] TCEs are the most commonly used in clinical practice, simultaneously binding to antigens on tumor cells and the CD3 subunit on T cells. This dual binding recruits T cells to the tumor site, where they become activated and undergo degranulation, ultimately leading to tumor cell elimination.[26 27] Previous studies have demonstrated their substantial efficacy in various hematologic malignancies, including targeting CD19 in ALL, CD20 in B-cell non-Hodgkin's lymphoma, and BCMA and GPRC5D in multiple myeloma.[28–32] However, similar to CAR-T therapy, the safety of BsAbs is also of concern. In this comprehensive pharmacovigilance analysis, we summarized the AEs of BsAb products. We identified 108 cases of SPMs among 10,280 recipients, with a notable CFR (29.63%), which exceeds the proportion observed in CRS or fever. The high proportion of serious outcomes observed in SPMs post-BsAbs therapy is a stark reminder of the potential dark side of targeted immunotherapies. Moreover, the annual reports consistently showed that SPMs accounted for a stable proportion of approximately 1–2% over the past 8 years, indicating that SPMs have remained a persistent issue and impose a significant burden on patients. While these agents have revolutionized cancer treatment, offering hope to patients with limited therapeutic options, the paradigm of "collateral damage" in the form of SPMs cannot be overlooked. Additionally, our analysis revealed distinct patterns of SPM development linked to different BsAb products: myeloid leukemias and non-Hodgkin's lymphoma were more common among blinatumomab recipients, while solid malignancies were more frequent in those treated with teclistamab. This implies that the occurrence of SPMs may be related to the specific targets of BsAbs.

Our study employed a robust methodology, using disproportionality analysis with ROR, PRR, and BCPNN to identify a preferential association of specific BsAbs with SPMs. Myelodysplastic syndromes, myeloid leukemias, non-Hodgkin's lymphoma, soft tissue neoplasms, gastrointestinal neoplasms, hepatobiliary neoplasms and respiratory tract cancers were identified as positive signals using the above methods. The consistency across

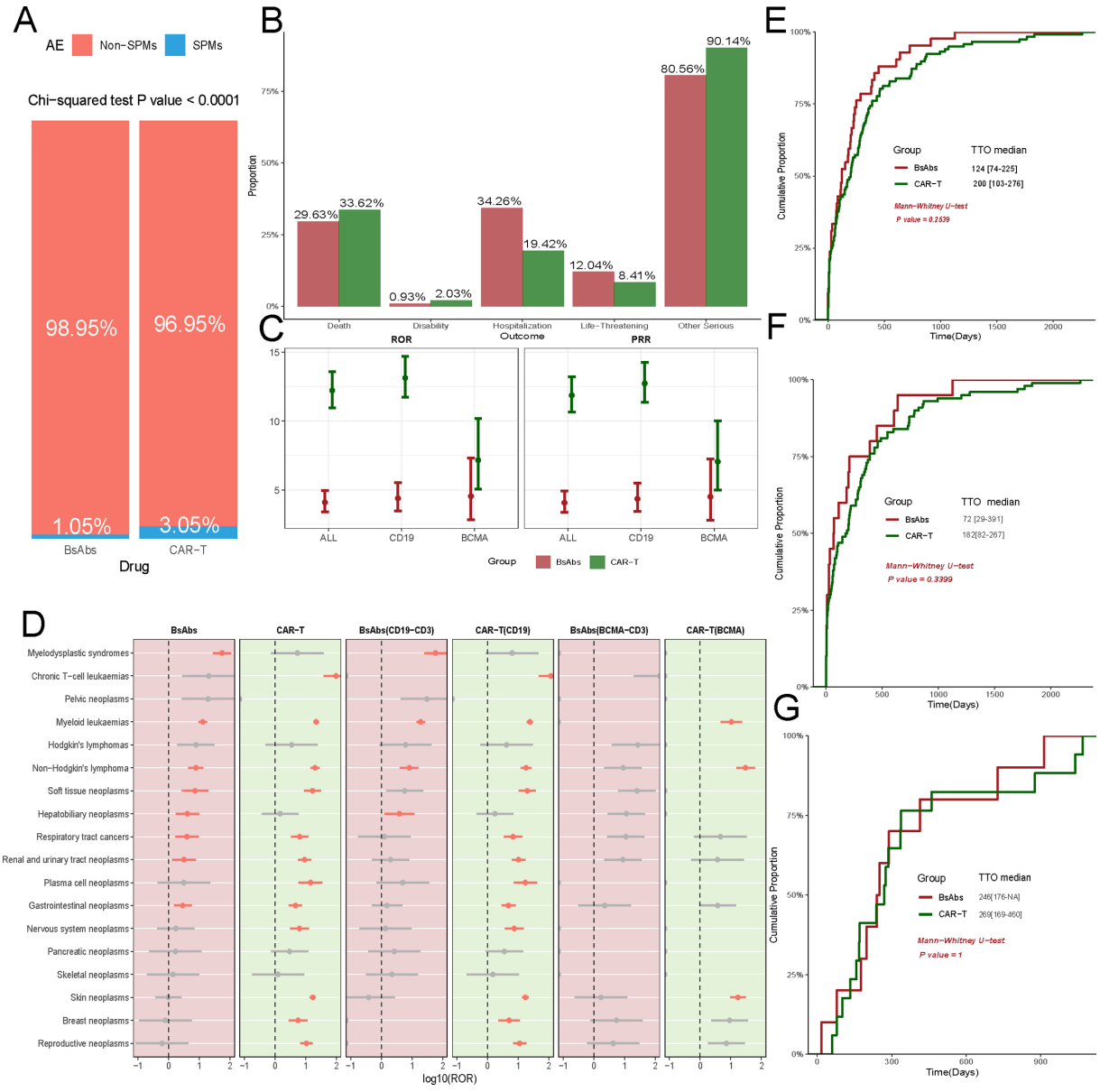

Figure 4 Comparative analysis of SPMs between BsAbs and CAR-T therapies. (A) The proportion of SPMs after BsAbs and CAR-T treatment. (B) The outcomes of SPMs after BsAbs and CAR-T treatment. (C) Signal comparison between BsAbs and CAR-T based on ROR and PRR. The error bars show the 95% CI of the ROR and PRR. (D) Forest plot presenting ROR values of SPMs with significant signals across different targets between BsAbs and CAR-T in FAERS. The error bars show the 95% CI of the ROR. Red signifies a significant positive signal, whereas gray denotes insignificance. (E, F and G) The cumulative distribution curve described the onset time difference of SPMs between BsAbs and CAR-T, including all targets (E), CD19 target (F) and BCMA target (G). AE, adverse event; BCMA, B-cell maturation antigen; BsAbs, bispecific antibodies; CAR, chimeric antigen receptor; FAERS, Food and Drug Administration's Adverse Event Reporting System; PRR, proportional reporting ratio; ROR, reporting OR; SPMs, secondary primary malignancies; TTO, time-to-onset.

these metrics reinforces the robustness of our findings. Additionally, we employed logistic regression to adjust for the effects of covariates, including age, sex, weight, and region, further confirming that BsAbs therapy is a significant risk factor for the development of SPMs. By adjusting for age, we partially mitigated survivorship bias, as age may act as a proxy for survival time and the cumulative risk of SPMs. However, we recognize that this adjustment may not fully eliminate the influence of survivorship bias. The FAERS database lacks detailed data on patient survival time, a limitation that precludes a direct and comprehensive assessment of how prolonged survival contributes to the observed association between BsAbs therapy and SPMs. Although our study provides an initial characterization of SPMs following BsAbs therapy, the observed association should be interpreted in light of the FAERS database's limitations and the survival benefits conferred by immunotherapy.

In the subgroup analysis comparing the SPM profiles of the CD19-CD3, CD20-CD3, BCMA-CD3 and other BsAbs types (including EGFR-MET, gp100-HLA-CD3, GPRC5D-CD3) recipients, the CD19-CD3 subgroup

showed almost identical SPM profile to the overall group analysis. Meanwhile, significantly increased risks of gastrointestinal neoplasms were observed following CD20-CD3 BsAbs. For other BsAbs types, non-Hodgkin's lymphoma and myeloid leukemias were also identified, although these findings did not reach statistical significance. These differences might result from the relatively later market approval of amivantamab, tebentafusp and talquetamab, which were officially approved by the FDA in 2021, 2022, and 2023, respectively.[33–35] The number of SPM cases associated with BsAbs used in solid tumors, such as amivantamab and tebentafusp, was lower than those associated with BsAbs used in hematologic malignancies, which may explain the absence of positive signals for other BsAb types.

Using TTO analysis, we discerned that the onset of SPMs in BsAbs recipients occurred earlier than in non-recipients, suggesting a potential causative link between BsAbs therapy and the development of SPMs. Notably, within the BsAbs recipient cohort, patients treated for more than 3 months exhibited a delayed onset of SPMs compared with those treated for 3 months or less. This apparent discrepancy may arise from clinical practices that cease BsAbs administration on SPMs diagnosis, potentially skewing the perception of SPMs onset timing. However, our findings indirectly delineate a critical temporal window for SPM development after BsAbs treatment, as 80% of SPMs occur within the first year. This underscores the clinical necessity for proactive and stringent early detection and intervention strategies for SPMs within this period. Furthermore, TTO analysis did not demonstrate any statistically significant differences across various BsAb products, ages, and genders, indicating that a uniform time frame and similar strategies can be employed for the early identification of SPMs across diverse patient populations. Remarkably, our study identified a weight-specific response to SPM events post-BsAbs treatment, with patients weighing less than 60 kg demonstrating an earlier onset of SPMs compared with those over 60 kg. The etiology of low body weight is complex and multifactorial, potentially interrelated with the tumor itself or the impact of treatment regimen. We postulate that underweight patients are more likely to experience a decline in immune function due to suboptimal nutritional status, which may affect the effectiveness of immunotherapies and increase their risk of developing SPMs.[36–40]

Our comparative analysis of BsAbs and CAR-T therapies demonstrated that while the risk of developing SPMs was lower with BsAb treatment compared with CAR-T. This difference may be attributed to several factors. First, CAR-T therapy involves viral vector integration into the host genome, which increases the risk of transgene-positive T-cell lymphomas or other transgene-positive tumors—a risk not associated with BsAbs therapy.[41] Additionally, lymphodepleting chemotherapy administered prior to CAR-T infusion may impair immune surveillance, thereby elevating the risk of SPMs post-CAR-T, particularly in patients with pre-existing genetic susceptibility.[41] In contrast, BsAbs therapy typically does not require lymphodepletion, potentially reducing this specific risk factor. Regarding BsAbs, their short half-life necessitates prolonged intravenous infusion (repeated dosing) to achieve stable serum levels over time, which enhances antitumor efficacy.[26 42] This prolonged administration may lead to cumulative immune activation, sustained inflammation, and other toxicities, potentially promoting the development of SPMs. Although the risk of developing SPMs is lower with BsAbs compared with CAR-T, the serious outcomes associated with SPMs were comparable between the two treatments, highlighting the need for vigilant clinical attention and monitoring. Therefore, we appeal to ongoing clinical trials of BsAbs, as well as clinicians treating patients with BsAbs, to report any newly diagnosed cancers. Additionally, we recommend that patients receiving these therapies and participants in clinical trials undergo regular monitoring for new cancers. Furthermore, the event-onset time and pattern of SPMs showed no statistical difference between CAR-T and BsAbs therapies, suggesting that early detection and intervention strategies for SPMs following BsAbs therapy could benefit from insights gained through the CAR-T experience. Our findings underline the potential value of developing standardized early detection protocols applicable to both CAR-T and BsAbs therapies, which could ultimately improve clinical outcomes for patients at risk of developing SPMs.

The mechanisms underlying SPMs following BsAbs therapy have not yet been the focus of dedicated research. Common factors associated with SPMs after cancer treatment include chemotherapy, radiation therapy, oncogenic viral infections, and immunosuppression following hematopoietic stem cell transplantation. BsAbs are used as second or third-line (non-first-line) treatment options for various hematologic malignancies. Many patients receiving BsAbs therapy have previously undergone multiple rounds of chemotherapy, radiation therapy, stem cell transplantation, and even CAR-T therapy. These treatments can have long-term effects on the immune system and may increase the risk of developing SPMs.[43] Therefore, the impact of prior treatments on the risk of SPMs following BsAbs therapy should not be overlooked. The patient's previous treatment history has led to an immunosuppressive state and an imbalance in immune homeostasis, and BsAbs therapy may further amplify such immune damage through synergistic effects, thereby increasing the risk of SPM and accelerating their onset. In addition, pre-existing uncertain potential clonal hematopoiesis (CHIP) and mixed lineage leukemia may make patients more susceptible to developing SPMs when exposed to genotoxic stress and immune modulation.[44–47] Prospective studies incorporating comprehensive genomic profiling and biomarker assessments would be instrumental in confirming the interplay between pre-existing CHIP clones, therapy-induced inflammation, and the development of SPMs after BsAbs therapy. Moreover,

according to the TTO analysis, the time to appearance of SPMs in BsAb recipients was significantly earlier than in non-recipients, and the median onset time of SPMs in our study did not fully align with existing reports of SPMs following chemotherapy, radiation, or transplantation.[48 49] Therefore, SPMs following BsAbs treatment may have causes independent of the aforementioned treatment strategies. On the one hand, BsAbs recruit a large number of immune cells, particularly T lymphocytes, to respond to and eliminate FPMs. This recruitment can lead to a "plundering" of T cells from the body, which are dedicated to combating FPMs, leaving only a small number of T lymphocytes available to monitor the development of SPMs. On the other hand, previous studies have shown that overactivation of immune cells and the subsequent release of large amounts of immune factors can, in turn, damage these cells, particularly lymphocytes.[50 51] BsAbs can lead to the overactivation of immune cells and the release of immune factors, which may cause T cells to eventually become exhausted or contribute to immune cell damage, as evidenced by CRS, a common adverse reaction following BsAbs treatment. In addition, chronic inflammation, resulting in immune suppression or disorders, creates a microenvironment that favors tumor development, promoting the growth of potential malignant clones.[44] These create an "immune window" in the body, establishing an immune ecology conducive to the occurrence and development of SPMs. However, this hypothesis of "T cell plundering" requires confirmation through future research.

While our FAERS-based analysis systematically characterizes SPMs after BsAbs therapy, the observed CFRs require cautious interpretation due to inherent limitations of spontaneous reporting. FAERS data are prone to reporting bias, with severe or fatal outcomes likely overrepresented, alongside incomplete reporting and potential duplicates, which may inflate apparent mortality rates. Thus, the elevated CFRs (eg, for CRS)—exceeding the mortality rates in clinical trials or real-world studies—likely reflect this bias rather than true population risk. Prospective cohort studies are needed to validate these findings and refine SPM risk estimates post-BsAbs therapy.

Limitations

Several limitations of this study warrant mention. First, FAERS data is limited to BsAbs recipients who experienced BsAbs-associated AEs, rather than all BsAbs recipients, which precluded an estimation of the overall incidence of BsAbs-related SPMs. Second, given that certain BsAb products have been recently approved, further and larger-scale pharmacovigilance studies are necessary as more data become available. This is particularly true for newer BsAb products, for which limited data currently exist. Third, the FAERS database primarily reflects populations from the Americas, with a notable under-representation of participants from other continents, particularly Africa. This geographic disparity may contribute to an underestimation of the risk of BsAbs-related SPMs in populations from these under-represented regions. Future research should seek to include data from these areas to more accurately evaluate the risk of BsAbs-related SPMs in diverse populations. Lastly, like all observational studies, causality cannot be inferred from our analyses. Confirming the causal nature of these signals will require further corroboration by independent sources of data and potentially mechanistic insight into BsAbs-related SPMs.

CONCLUSION

Our comprehensive analysis of real-world data highlights the significance of SPMs as a relatively infrequent but serious AE following BsAbs therapy. Enhancing the benefit-risk profile of BsAbs therapy is crucial to ensuring the safety and efficacy of this novel immunotherapy. Future research should focus on extensive clinical observations and experimental studies to validate our findings and refine SPMs screening and clinical strategies for BsAb recipients.

Author affiliations
[1]Department of Hematology, Beijing Tongren Hospital, Capital Medical University, Beijing, China
[2]Department of Hematology, Nanfang Hospital, Southern Medical University, Guangzhou, China
[3]Department of Radiology, Shunde Hospital, Southern Medical University, Foshan, China
[4]The First School of Clinical Medicine, Guangdong Medical University, Zhanjiang, China
[5]Stomatological Hospital, School of Stomatology, Southern Medical University, Guangzhou, China
[6]Department of General Medicine, Maoming People's Hospital, Maoming, China

Contributors LW and HZ designed the study, interpreted data, and revised the manuscript. XL, BLu and BLi performed statistical analysis, interpreted data, and wrote the manuscript. DL, JG, WL, ST, ZC, XZ, ZJ, TL and KC provided data analysis and contributed to manuscript revision. All authors have read and approved the final version of the manuscript. LW and HZ are the guarantors and take full responsibility for the finished work and the conduct of the study.

Funding This work was supported by grants from the National Natural Science Foundation of China (Nos. 82170181) and Beijing Physician Scientist Training Project (BJPSTP-2024-01) to LW.

Competing interests No, there are no competing interests.

Patient consent for publication Not applicable.

Ethics approval This study was exempted from the institutional review board's approval because it used anonymized data in a public database.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information. The datasets presented in this study can be found in the FAERS online repositories (https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html).

ORCID iDs
Xiaojie Liang http://orcid.org/0000-0003-4135-3155
Baiwei Luo http://orcid.org/0000-0002-0374-5724
Bingyu Lin http://orcid.org/0009-0002-3284-5887
Dan Liu http://orcid.org/0009-0004-0858-0561
Jia Guo http://orcid.org/0009-0000-6770-7359
Weixiang Lu http://orcid.org/0009-0001-1034-7425
Shengyu Tian http://orcid.org/0009-0009-6374-1096
Zihong Cai http://orcid.org/0009-0005-4848-9508
Xinyu Zhou http://orcid.org/0009-0004-5342-4664
Zhihao Jin http://orcid.org/0009-0003-9804-9549
Tong Li http://orcid.org/0009-0003-8963-405X
Keren Chen http://orcid.org/0000-0002-2386-3541
Hongsheng Zhou http://orcid.org/0000-0002-4888-7021
Liang Wang http://orcid.org/0000-0001-6140-914X

REFERENCES

1 Neelapu SS, Locke FL, Bartlett NL, *et al*. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. *N Engl J Med* 2017;377:2531–44.
2 Kersten MJ, Spanjaart AM, Thieblemont C. CD19-directed CAR T-cell therapy in B-cell NHL. *Curr Opin Oncol* 2020;32:408–17.
3 Labrijn AF, Janmaat ML, Reichert JM, *et al*. Bispecific antibodies: a mechanistic review of the pipeline. *Nat Rev Drug Discov* 2019;18:585–608.
4 Klein C, Brinkmann U, Reichert JM, *et al*. The present and future of bispecific antibodies for cancer therapy. *Nat Rev Drug Discov* 2024;23:301–19.
5 van de Donk NWCJ, Zweegman S. T-cell-engaging bispecific antibodies in cancer. *Lancet* 2023;402:142–58.
6 Trabolsi A, Arumov A, Schatz JH. Bispecific antibodies and CAR-T cells: dueling immunotherapies for large B-cell lymphomas. *Blood Cancer J* 2024;14:27.
7 Holstein SA, Grant SJ, Wildes TM. Chimeric Antigen Receptor T-Cell and Bispecific Antibody Therapy in Multiple Myeloma: Moving Into the Future. *J Clin Oncol* 2023;41:4416–29.
8 Hamilton MP, Sugio T, Noordenbos T, *et al*. Risk of Second Tumors and T-Cell Lymphoma after CAR T-Cell Therapy. *N Engl J Med* 2024;390:2047–60.
9 Ghilardi G, Fraietta JA, Gerson JN, *et al*. T cell lymphoma and secondary primary malignancy risk after commercial CAR T cell therapy. *Nat Med* 2024;30:984–9.
10 Zhou Z, Zhang G, Xu Y, *et al*. The underlying mechanism of chimeric antigen receptor (CAR)-T cell therapy triggering secondary T-cell cancers: Mystery of the Sphinx? *Cancer Lett* 2024;597:217083.
11 Ozdemirli M, Loughney TM, Deniz E, *et al*. Indolent CD4+ CAR T-Cell Lymphoma after Cilta-cel CAR T-Cell Therapy. *N Engl J Med* 2024;390:2074–82.
12 Levine BL, Pasquini MC, Connolly JE, *et al*. Unanswered questions following reports of secondary malignancies after CAR-T cell therapy. *Nat Med* 2024;30:338–41.
13 Furlow B. FDA investigates risk of secondary lymphomas after CAR-T immunotherapy. *Lancet Oncol* 2024;25:21.
14 Goebeler ME, Stuhler G, Bargou R. Bispecific and multispecific antibodies in oncology: opportunities and challenges. *Nat Rev Clin Oncol* 2024;21:539–60.
15 Philipp N, Kazerani M, Nicholls A, *et al*. T-cell exhaustion induced by continuous bispecific molecule exposure is ameliorated by treatment-free intervals. *Blood* 2022;140:1104–18.
16 Meermeier EW, Welsh SJ, Sharik ME, *et al*. Tumor burden limits bispecific antibody efficacy through T cell exhaustion averted by concurrent cytotoxic therapy. *Blood Cancer Discov* 2021;2:354–69.
17 Khaleel MA, Khan AH, Ghadzi SMS, *et al*. A Standardized Dataset of a Spontaneous Adverse Event Reporting System. *Healthcare (Basel)* 2022;10:420.
18 Yu Y, Chen J, Li D, *et al*. Systematic Analysis of Adverse Event Reports for Sex Differences in Adverse Drug Events. *Sci Rep* 2016;6:24955.
19 Rothman KJ, Lanes S, Sacks ST. The reporting odds ratio and its advantages over the proportional reporting ratio. *Pharmacoepidemiol Drug Saf* 2004;13:519–23.
20 Bate A, Lindquist M, Edwards IR, *et al*. A Bayesian neural network method for adverse drug reaction signal generation. *Eur J Clin Pharmacol* 1998;54:315–21.
21 Bate A. Bayesian confidence propagation neural network. *Drug Saf* 2007;30:623–5.
22 Zhang X, Jiang Y, Guo Y, *et al*. Safety evaluation of ceftazidime/avibactam based on FAERS database. *Infection* 2024;52:2195–205.
23 Brudno JN, Kochenderfer JN. Current understanding and management of CAR T cell-associated toxicities. *Nat Rev Clin Oncol* 2024;21:501–21.
24 Bond DA, Huang Y, Fisher JL, *et al*. Second cancer incidence in CLL patients receiving BTK inhibitors. *Leukemia* 2020;34:3197–205.
25 Jones JR, Cairns DA, Menzies T, *et al*. Maintenance lenalidomide in newly diagnosed transplant eligible and non-eligible myeloma patients; profiling second primary malignancies in 4358 patients treated in the Myeloma XI Trial. *EClinicalMedicine* 2023;62:102099.
26 Goebeler ME, Bargou RC. T cell-engaging therapies — BiTEs and beyond. *Nat Rev Clin Oncol* 2020;17:418–34.
27 Fenis A, Demaria O, Gauthier L, *et al*. New immune cell engagers for cancer immunotherapy. *Nat Rev Immunol* 2024;24:471–86.
28 Kantarjian H, Stein A, Gökbuget N, *et al*. Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia. *N Engl J Med* 2017;376:836–47.
29 Hutchings M, Morschhauser F, Iacoboni G, *et al*. Glofitamab, a Novel, Bivalent CD20-Targeting T-Cell–Engaging Bispecific Antibody, Induces Durable Complete Remissions in Relapsed or Refractory B-Cell Lymphoma: A Phase I Trial. *JCO* 2021;39:1959–70.
30 Liu X, Zhao J, Guo X, *et al*. CD20 × CD3 bispecific antibodies for lymphoma therapy: latest updates from ASCO 2023 annual meeting. *J Hematol Oncol* 2023;16:90.
31 Usmani SZ, Garfall AL, van de Donk N, *et al*. Teclistamab, a B-cell maturation antigen × CD3 bispecific antibody, in patients with relapsed or refractory multiple myeloma (MajesTEC-1): a multicentre, open-label, single-arm, phase 1 study. *Lancet* 2021;398:665–74.
32 Chari A, Minnema MC, Berdeja JG, *et al*. Talquetamab, a T-Cell-Redirecting GPRC5D Bispecific Antibody for Multiple Myeloma. *N Engl J Med* 2022;387:2232–44.
33 Syed YY. Amivantamab: First Approval. *Drugs (Abingdon Engl)* 2021;81:1349–53.
34 Dhillon S. Tebentafusp: First Approval. *Drugs (Abingdon Engl)* 2022;82:703–10.
35 Keam SJ. Talquetamab: First Approval. *Drugs (Abingdon Engl)* 2023;83:1439–45.
36 Ahmed M, von Itzstein MS, Sheffield T, *et al*. Association between body mass index, dosing strategy, and efficacy of immune checkpoint inhibitors. *J Immunother Cancer* 2021;9:e002349.
37 Bader JE, Wolf MM, Lupica-Tondo GL, *et al*. Obesity induces PD-1 on macrophages to suppress anti-tumour immunity. *Nature New Biol* 2024;630:968–75.
38 Murphy WJ, Longo DL. The Surprisingly Positive Association Between Obesity and Cancer Immunotherapy Efficacy. *JAMA* 2019;321:1247–8.
39 Naik GS, Waikar SS, Johnson AEW, *et al*. Complex inter-relationship of body mass index, gender and serum creatinine on survival: exploring the obesity paradox in melanoma patients treated with checkpoint inhibition. *J Immunother Cancer* 2019;7:89.
40 Sanchez A, Furberg H, Kuo F, *et al*. Transcriptomic signatures related to the obesity paradox in patients with clear cell renal cell carcinoma: a cohort study. *Lancet Oncol* 2020;21:283–93.
41 Patel SA, Spiegel JY, Dahiya S. Second Primary Cancer After Chimeric Antigen Receptor-T-Cell Therapy: A Review. *JAMA Oncol* 2025;11:174–81.
42 Tian Z, Liu M, Zhang Y, *et al*. Bispecific T cell engagers: an emerging therapy for management of hematologic malignancies. *J Hematol Oncol* 2021;14:75.
43 Singhal D, Kutyna MM, Hahn CN, *et al*. Therapy-Related Myeloid Neoplasms: Complex Interactions among Cytotoxic Therapies, Genetic Factors, and Aberrant Microenvironment. *Blood Cancer Discov* 2024;5:400–16.
44 Belizaire R, Wong WJ, Robinette ML, *et al*. Clonal haematopoiesis and dysregulation of the immune system. *Nat Rev Immunol* 2023;23:595–610.
45 Coorens THH, Collord G, Treger TD, *et al*. Clonal origin of KMT2A wild-type lineage-switch leukemia following CAR-T cell and blinatumomab therapy. *Nat Cancer* 2023;4:1095–101.

46 Zhou T, Curry CV, Khanlari M, *et al*. Genetics and pathologic landscape of lineage switch of acute leukemia during therapy. *Blood Cancer J* 2024;14:19.
47 Granja JM, Klemm S, McGinnis LM, *et al*. Single-cell multiomic analysis identifies regulatory programs in mixed-phenotype acute leukemia. *Nat Biotechnol* 2019;37:1458–65.
48 Morton LM, Saber W, Baker KS, *et al*. National Institutes of Health Hematopoietic Cell Transplantation Late Effects Initiative: The Subsequent Neoplasms Working Group Report. *Biol Blood Marrow Transplant* 2017;23:367–78.
49 Inamoto Y, Shah NN, Savani BN, *et al*. Secondary solid cancer screening following hematopoietic cell transplantation. *Bone Marrow Transplant* 2015;50:1013–23.
50 O'Toole RF. The interface between COVID-19 and bacterial healthcare-associated infections. *Clin Microbiol Infect* 2021;27:1772–6.
51 Reina-Campos M, Scharping NE, Goldrath AW. CD8+ T cell metabolism in infection and cancer. *Nat Rev Immunol* 2021;21:718–38.