



HAL
open science

Characteristics and incidence of infections in patients with multiple myeloma treated by bispecific antibodies: a national retrospective study

Aurélie Jourdes, Elise Cellerin, Cyrille Touzeau, Stéphanie Harel, Blandine Denis, Guillaume Escure, Emmanuel Faure, Simon Jamard, Francois Danion, Cécile Sonntag, et al.

► To cite this version:

Aurélie Jourdes, Elise Cellerin, Cyrille Touzeau, Stéphanie Harel, Blandine Denis, et al.. Characteristics and incidence of infections in patients with multiple myeloma treated by bispecific antibodies: a national retrospective study. *Clinical Microbiology and Infection*, 2024, 30 (6), pp.764-771. 10.1016/j.cmi.2024.02.023 . hal-04916309

HAL Id: hal-04916309

<https://hal.science/hal-04916309v1>

Submitted on 28 Jan 2025

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution 4.0 International License



Original article

Characteristics and incidence of infections in patients with multiple myeloma treated by bispecific antibodies: a national retrospective study

Aurélie Jourdes¹, Elise Cellerin², Cyrille Touzeau³, Stéphanie Harel⁴, Blandine Denis⁵, Guillaume Escure⁶, Emmanuel Faure^{6,7}, Simon Jamard⁸, Francois Danion^{9,10}, Cécile Sonntag¹¹, Florence Ader^{12,13}, Lionel Karlin¹⁴, Sarah Soueges¹², Clarisse Cazelles^{15,16}, Clémentine de La Porte des Vaux¹⁷, Laurent Frenzel^{15,18}, Fanny Lanternier^{17,19}, Xavier Brousse²⁰, Titouan Cazaubiel^{21,22}, Pierre Berger²³, Aude Collignon²⁴, Mathieu Blot^{25,26,27}, Andrea Pieragostini²⁸, Morgane Charles²⁹, Carine Chaletex³⁰, Alexis Redor³¹, Virginie Roland³², Tom Cartau³³, Margaret Macro³⁴, Thomas Chalopin², Nicolas Vallet^{2,35}, Aurore Perrot^{20,36}, Guillaume Martin-Blondel^{1,37,*}, on behalf of the G2I and the IFM networks

¹ Service de Maladies Infectieuses et Tropicales, Centre Hospitalo-universitaire (CHU) de Toulouse, France

² Service d'hématologie, Centre Hospitalo-universitaire (CHU) de Tours, France

³ Service d'hématologie, Centre Hospitalo-universitaire (CHU) Hôtel Dieu, Nantes, France

⁴ Service d'immuno-hématologie, Hôpital St-Louis, AP-HP, Paris, France

⁵ Service de Maladies Infectieuses et Tropicales, Hôpital St-Louis, AP-HP, Paris, France

⁶ Service d'hématologie, Centre Hospitalo-universitaire (CHU) de Lille, France

⁷ U1019-UMR 9017-Centre d'Infection et d'Immunité de Lille, INSERM, Centre National de la Recherche Scientifique, Institut Pasteur de Lille, Université de Lille, Lille, France

⁸ Service de Médecine Infectieuse et Tropicale, Centre Hospitalo-Universitaire (CHU) de Tours, France

⁹ Service de Maladies Infectieuses et Tropicales, Les Hôpitaux Universitaires de Strasbourg, Strasbourg, Grand Est, France

¹⁰ Laboratoire d'Immuno-rhumatologie Moléculaire UMR_S 1109, INSERM, Strasbourg, Grand Est, France

¹¹ Service d'hématologie, Institut de Cancérologie de Strasbourg Europe (ICANS), Strasbourg, France

¹² Département des Maladies Infectieuses et Tropicales, Hospices Civils de Lyon, Lyon, France

¹³ Centre International de Recherche en Infectiologie (CIRI), INSERM 1111, Université Claude Bernard Lyon 1, CNRS, UMR5308, École Normale Supérieure de Lyon, Univ Lyon, Lyon, France

¹⁴ Service d'hématologie, Centre Hospitalier Lyon-Sud, Lyon, France

¹⁵ Service d'hématologie, Hôpital Necker-Enfants Malades, AP-HP, Paris, France

¹⁶ Institut Cochin, Université de Paris, CNRS UMR8104, INSERM U1016, Paris, France

¹⁷ Service de Maladies Infectieuses et Tropicales, Hôpital Necker-Enfants Malades, AP-HP, Paris, France

¹⁸ CEREMAST, Institut Imagine, INSERM U1163, AP-HP, Hôpital Necker-Enfants Malades, Université Paris Centre, Paris, France

¹⁹ Institut Pasteur, Université Paris Cité, Centre National de Référence Mycoses Invasives et Antifongiques, Groupe de Recherche Translationnelle en Mycologie, Département de Mycologie, Paris, Île-de-France, France

²⁰ Service de Maladies Infectieuses et Tropicales, Centre Hospitalo-universitaire (CHU) de Bordeaux, France

²¹ Service d'hématologie, Centre Hospitalo-universitaire (CHU) de Bordeaux, France

²² Equipe Génomique et Immunologie du Myélome Multiple, Centre de Recherche en Cancérologie de Toulouse INSERM U1037, Université Paul Sabatier, Toulouse, France

²³ Infectiologie Transversale, Institut Paoli-Calmettes, Marseille, France

²⁴ Service d'hématologie, Institut Paoli-Calmettes, Marseille, France

²⁵ Service de Maladies Infectieuses et Tropicales, Centre Hospitalo-universitaire (CHU) de Dijon-Bourgogne, France

²⁶ INSERM, Université de Bourgogne, CIC 1432, Module Épidémiologie Clinique, Dijon, France

²⁷ Equipe Lipness, INSERM LNC-UMR1231 et LabEx LipSTIC, Université de Burgundy, Dijon, France

²⁸ Service d'hématologie, Centre Hospitalo-universitaire (CHU) de Dijon-Bourgogne, France

²⁹ Service de Maladies Infectieuses et Tropicales, Centre Hospitalo-universitaire (CHU) d'Estaing, Clermont-Ferrand, France

³⁰ Service d'hématologie, Centre Hospitalo-universitaire (CHU) d'Estaing, Clermont-Ferrand, France

³¹ Service de Maladies Infectieuses et Tropicales, Centre Hospitalier de Perpignan, France

³² Service d'hématologie, Centre Hospitalier de Perpignan, France

* Corresponding author. Guillaume Martin-Blondel, Service des maladies infectieuses et tropicales, CHU de Toulouse Purpan, Place du Dr Joseph Baylac, 31300 Toulouse, France.

E-mail address: martin-blondel.g@chu-toulouse.fr (G. Martin-Blondel).

³³⁾ Service de Maladies Infectieuses et Tropicales, Centre Hospitalo-universitaire (CHU) Côte de Nacre, Caen, France

³⁴⁾ Service d'hématologie, Institut bas Normand d'Hématologie, CHU Caen Normandie, Caen, France

³⁵⁾ Equipe INSERM U1069 N2COx, Groupe LNOx, Université de Tours, France

³⁶⁾ Service d'hématologie, Centre Hospitalo-universitaire (CHU) de Toulouse, Institut Universitaire du Cancer de Toulouse-Oncopole (IUCT-O), Toulouse, France

³⁷⁾ Institut Toulousain des Maladies Infectieuses et Inflammatoires (Infinity) INSERM, Université Toulouse III, Toulouse, France

ARTICLE INFO

Article history:

Received 21 November 2023

Received in revised form

10 February 2024

Accepted 27 February 2024

Available online 1 March 2024

Editor: C. Roy

Keywords:

Adverse event

Bispecific antibodies

Epidemiology

Infections

Multicentric

Multiple myeloma

Retrospective

ABSTRACT

Objectives: Bispecific antibodies (BsAbs) are an effective treatment used in relapsed or refractory multiple myeloma. Despite a well-tolerated safety profile, infectious events appear to be frequent in clinical trials. Real-world data on epidemiology, characteristics, risk factors, and outcomes of infections in patients treated with BsAb are still needed.

Methods: A retrospective, multicentre study in BsAb-treated patients with multiple myeloma was performed in 14 French centres from December 2020 to February 2023. The primary objective was to describe the incidence of infections that required hospitalization, specific treatment, or adaptation in BsAb administration.

Results: Among 229 patients with multiple myeloma treated with BsAb, 153 (67%) received teclistamab, 47 (20%) received elranatamab, and 29 (13%) talquetamab. We reported a total of 234 infections, including 123 (53%) of grade of ≥ 3 . Predominant infections affected the respiratory tract ($n = 116$, 50%) followed by bacteraemias ($n = 36$, 15%). The hospitalization rate was 56% ($n = 131$), and 20 (9%) infections resulted in death. Global cumulative incidence of the first infection was 70% in all patients, 73% in patients treated with B-cell maturation antigen-targeting, and 51% with GPRC5D-targeting BsAb. In univariate analyses, corticosteroids for cytokine release syndrome (CRS)/immune effector cell-associated neurotoxicity syndrome (ICANS) were associated with a higher risk of first infection (HR = 2.13; 95% CI, 1.38–3.28), whereas GPRC5D-targeting BsAb and anti-bacterial prophylaxis were associated with a lower risk (HR = 0.53; 95% CI, 0.3–0.94 and HR = 0.65; 95% CI, 0.46–0.9). Fine and Gray multivariate model found that only corticosteroids for CRS/ICANS were correlated with a higher risk of first infection (HR = 2.01; 95% CI, 1.27–3.19).

Discussions: The implementation of preventive measures that aim to mitigate the risk of infection under BsAb is pivotal, notably in patients who received corticosteroids for CRS/ICANS. **Aurélien Jourdes, Clin Microbiol Infect 2024;30:764**

© 2024 The Authors. Published by Elsevier Ltd on behalf of European Society of Clinical Microbiology and Infectious Diseases. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

Introduction

Outcomes of multiple myeloma (MM) have improved significantly since the advent of proteasome inhibitors (PIs), immunomodulatory agents (IMiDs), and anti-CD38 monoclonal antibodies [1]. However, MM remains incurable, and patients relapse and/or become refractory [2]. Immunotherapeutic approaches have been developed to harness the patient's immune system to eliminate the malignant plasma cells. These developments include chimeric antigen receptor (CAR)-T cell therapy, antibody–drug conjugates (ADC), and, more recently, bispecific antibodies (BsAb) [3].

Bispecific antibodies bind a target on the malignant plasma cells and on T-cells, which form an immunologic synapse and subsequent T-cell activation and tumour cell lysis [4]. The main BsAb used in MM targets the B-cell maturation antigen (BCMA), such as teclistamab and elranatamab, or the G-protein coupled receptor family C group 5 member D (GPRC5D) for talquetamab [5]. The BsAbs are increasingly used in relapsed or refractory MM (RR-MM) with promising results [6–8]. Several trials have highlighted BsAb-associated adverse events, such as cytokine release syndrome (CRS), cytopenia, hypogammaglobulinaemia, and infections [6–8]. A higher risk of severe infections and infection-related deaths was also reported in clinical trials [6–11]. Reported incidences of all-grade infections are 46% to 76%, of which 7% to 45% are grade 3 to 4 events [9,11,12]. Few real-world studies have been performed with only monocentric case-series [10,13] and a small-scale multicentric study [14].

Thus, we performed a real-world multicentre national study to describe characteristics of infections affecting the management of

patients treated with BCMA-targeting or GPRC5D-targeting BsAb and identify their risk factors.

Methods

Type of study and data sources

We performed a multicentre retrospective study in France through the Groupe Infection et Immunodépression network of the Société de pathologie infectieuse de langue française and the Intergroupe Francophone du Myélome network. Patients were identified in each participating centre. Clinical and biological data were extracted from electronic health records and collected on a standardized case report form.

Patients and events definitions

All patients with MM who received BsAb therapy between 1 December 2020 and 1 February 2023, were included. We reported infections occurring after the complete priming dose and up to 3 months after the interruption of treatment, whether there was a new therapeutic line or not. Infections were categorized as microbiologically-defined (MDI), clinically-defined (CDI), or fever of unknown focus (FUF) and severity graded according to published criteria [15,16]. The MDI was defined as a laboratory-isolated pathogen with a compatible clinical syndrome, CDI was defined by a compatible clinical syndrome without an isolated pathogen, and FUF was defined as the presence of fever and the absence of compatible microbiology or focal symptoms [15]. We

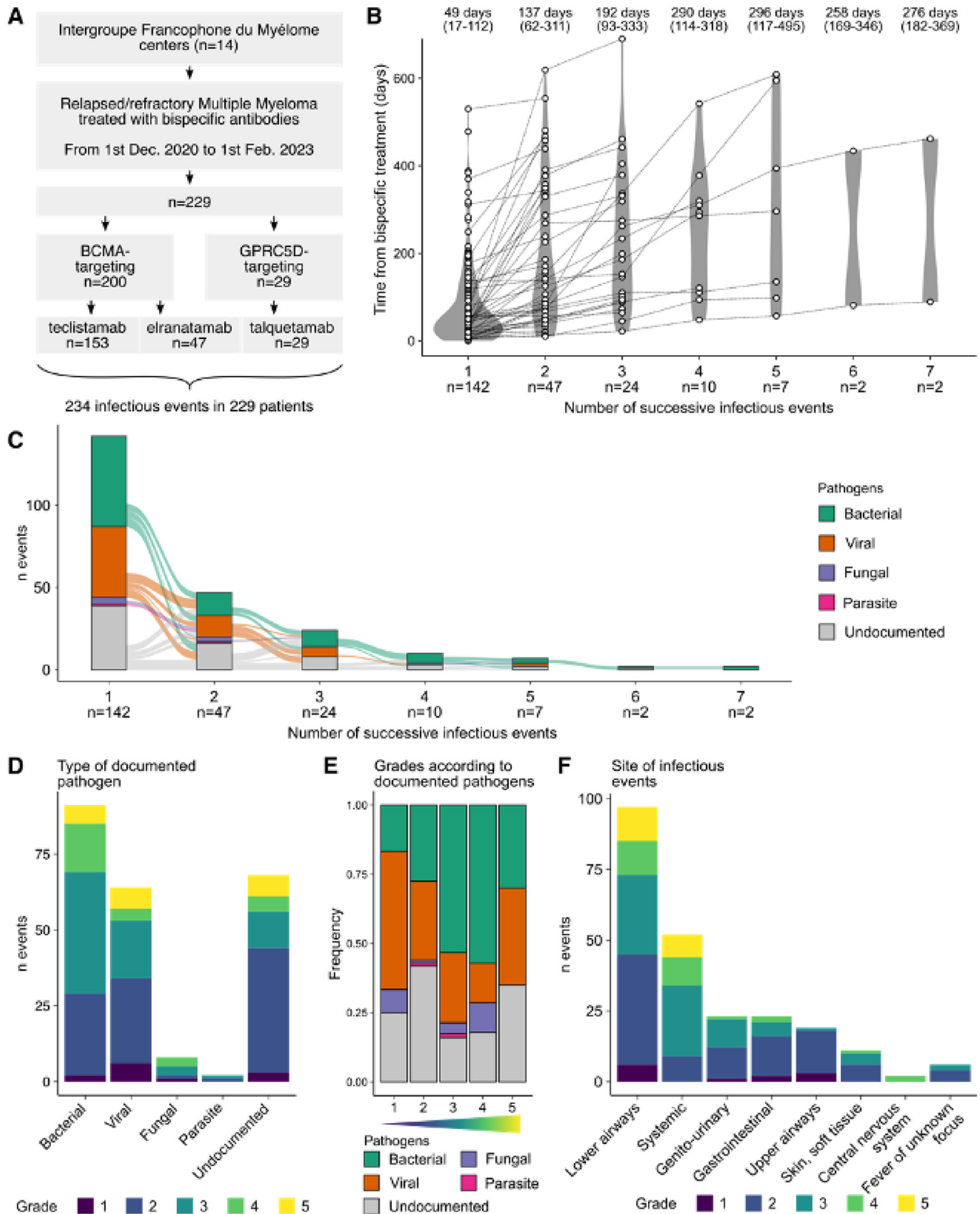


Fig. 1. Main characteristics of infections. (A) Flow diagram showing the study design and main groups of included patients. (B) Violin plots and dot plots depicting the time from bispecific antibody treatment to infections according to the number of successive infections. Each dot represents an infection, dotted gray lines connect two infections from the same patient. Median time to infection with the corresponding interquartile range are reported in the upper part of the plot. (C) Alluvial plot describing the successive infectious

only considered infections graded according to CTCAE (Common terminology criteria for adverse events) v5.0 [16] affecting the management of the patient because they required hospitalization, specific treatment or adaptation in BsAb administration (then called infection impacting patient management): grade 1 mild or asymptomatic infections which required no intervention but delayed the administration of the BsAb, grade 2 moderate infections which required minimal, local or noninvasive intervention; grade 3 severe or medically significant infections which required hospitalization or invasive intervention; grade 4 life-threatening infections; and grade 5 infections which contributed to death [16]. CRS, inducing fever and sometimes leading to hypotension or oxygen desaturation, and immune effector cell-associated neurotoxicity syndrome (ICANS) were defined according to published criteria [17]. Hypogammaglobulinaemia was assessed by subtracting out the monoclonal Ig and defined as Ig < 400 mg/dL. Patients with MM refractory to IMiDs, Pls, and antiCD38 monoclonal Abs, were referred to as triple-class refractory.

Ethical approval

The study was performed in accordance with Good Clinical Practice and the Declaration of Helsinki, approved by the ethical committee review board of the Société de pathologie infectieuse de langue française (n°IRB00011642) and covered by the MR-004 reference methodology (RnIPH 2023-47). In accordance with French law on ethics, patients were informed that their codified data would be used for the study. Patient's non-opposition to the use of the data and to publication was collected. All clinical data were recorded anonymously.

Statistical analysis

The primary objective was to describe the occurrence of all infections affecting patient management and detail the infections' characteristics. Secondary objectives were to describe cumulative incidences and identify variables associated with the occurrence of first infection. Continuous variables were reported with median and interquartile range (IQR) and categorical variables with number of patients and frequencies. Considering that variable distribution would unlikely fit a Gaussian distribution, nonparametric Mann-Whitney-Wilcoxon or Kruskal-Wallis tests were performed to compare continuous variables between two and three or more groups, respectively. Categorical variables were compared with Fisher exact test or χ^2 if appropriate. Infectious events were studied as time-dependent variables with the Fine and Gray model with death as a competing risk event. Exploratory univariate analyses were used to identify variables associated with infectious events. Then multivariate models were used to adjust computed hazard ratio (HR) and 95% CI. A p value of <0.05 was considered statistically significant. Data analyses were computed in an R environment built with Guix to allow transparency and reproducibility [18].

Data and code sharing

According to Findability, Accessibility, Interoperability, and Reuse principles all anonymized data and source code of analyses are provided in the following public repository: <https://gitlab.com/nivall/mbispid>, long term preserved on Software Heritage (<https://archive.softwareheritage.org/swh:1:dir:71e0b5b3335a04a43a22f3533068270dc85a6908>).

Results

Patients' characteristics

We identified 229 patients treated with BsAb in 14 centres with a median follow-up of 7 months (IQR: 4–12, Fig. 1[A]). Two hundred patients (87%) received BCMA-targeting BsAb (teclistamab [$n = 153$] or elranatamab [$n = 47$]) and 29 (13%) received GPR5D-targeting BsAb (talquetamab). The main baseline characteristics of the patients are presented in Table 1. At the end of follow-up, 74 patients (32%) had died.

Characteristics of infections impacting patient management

Among the 229 patients, 142 (62%) presented at least one infection affecting patient management with a median time from BsAb initiation of 49 days (IQR: 17–112) and a median number of infections per patient of 1.0 (range 1–7). A total of 234 infections affecting patient management occurred during the study period (Fig. 1[B] and [C]), of which 165 (71%) were MDI, 62 (26%) were CDI and 7 (3%) were FUF. The predominant localization was the respiratory tract ($n = 116/234$, 50%) followed by disseminated infections ($n = 52/234$, 22%) mainly through bacteraemias ($n = 36$, 15%) (Table 2).

One hundred and thirty-three (61%) infections occurred in patients with hypogammaglobulinaemia <400 mg/dL at the time of infection and 50 (21%) in patients under immunoglobulin substitution. Prophylaxis received by patients at time of infection is described in the Table S1.

Hospital admission was required in 131 (56%) infectious events with a median length stay of 10 days (range: 1–111). Intensive care unit (ICU) admission was required in 30 (13%) episodes. There was a total of 20 (9%) deaths attributed to infection. One hundred and twenty-three (53%) infections were grade 3 or higher (Fig. 1[D], [E], and [F]). All grade 4–5 or requiring ICU admission infections involved patients undergoing BCMA-targeting BsAb. Among the 234 infectious events, 103 (44%) had an effect on the course of MM treatment with discontinuation in 31 cases (13%), ≥ 14 days delayed administration in 70 cases (30%) and spacing or dose reduction in 2 cases (1%). Characteristics of first infections occurring in patients treated with corticosteroids for CRS/ICANS, and of patients admitted in ICU, are presented in the Tables S2 and S3, respectively.

Cumulative incidence and variables associated with first infections impacting patient management

Global cumulative incidence of first infection was 70% (30-days: 22.8%, 90-days: 43.1%, and 180-days: 55.5%), 73% (30-days: 23.7%, 90-days: 45.9%, and 180-days: 59.3%) in patients treated with BCMA-targeting BsAb and 51% (30-days: 17.2%, 90-days: 24.1%, and 180-days: 31%) with GPR5D-targeting BsAb (Fig. 2[A] and [B], Fig. S1).

Exploratory univariate analyses with Fine and Gray models with death before first infection as competing risk event revealed that corticosteroids treatment to manage CRS or ICANS was associated with a higher risk of first infection (HR = 2.13; 95% CI, 1.38–3.28),

events according to the pathogen documentation. (D) Stacked bar plot reporting the number of infections according to the type of pathogen. Plots are coloured according to the grade of the recorded event. (E) Stacked bar plot describing the frequency of each type of pathogen according to the grade of the infection. (F) Stacked bar plot illustrating the number of infections according to the identified site of infection. Systemic included bacteraemia, viraemia, fungaemia and infections affecting multiple organs. Plots are coloured according to the grade of the recorded event.

Table 1
Characteristics of the 229 MM patients on BsAb therapy

Variables	Total (n = 229)	BCMA-targeting BsAbs ^a (n = 200)	GPRC5D-targeting BsAb ^b (n = 29)
Age (y), median (range)	67 (38–85)	67 (38–85)	66 (49–83)
Women, n (%)	112 (49)	92 (46)	20 (69)
Immunohistochemical subtype, n (%)			
IgG	121/227 (53)	109/198 (55)	12/29 (41)
IgA	51/227 (22)	49/198 (25)	2/29 (7)
IgD	1/227 (1)	1/198 (1)	0/29 (0)
Light chain	54/227 (24)	39/198 (20)	15/29 (52)
Median prior lines of therapy ^c , (n = 225)	4.0 (0–15)	4.0 (0–15)	4.0 (1–9)
Triple-class refractory myeloma, n (%)	187 (82)	159 (80)	28 (97)
ACST, n (%)	149 (65)	96 (63)	30 (64)
ISS stage, n (%)			
I	69/182 (38)	61/158 (39)	8/24 (33)
II	62/182 (34)	53/158 (34)	9/24 (38)
III	51/182 (28)	44/158 (28)	7/24 (29)
R-ISS stage, n (%)			
I	33/134 (25)	32/122 (26)	1/12 (8.3)
II	73/134 (54)	66/122 (54)	7/12 (58)
III	28/134 (21)	24/122 (20)	4/12 (33)
All-grade CRS, n (%)	138 (60)	119 (60)	19 (66)
All-grade ICANS, n (%)	12 (5)	10 (5)	2 (7)
Corticosteroids for CRS/ICANS, n (%)	37/225 (16)	37/196 (19)	0/29 (0)
Tocilizumab for CRS/ICANS, n (%)	57/225 (25)	45/196 (23)	12/29 (41)
≥1 week of neutropaenia <0.5 × 10 ⁹ /L during BsAb treatment	19/114 (17)	18/109 (17)	1/5 (20)

Changes in denominators in the table indicate missing data. ACST, autologous stem cell transplant; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; ISS, international staging system; R-ISS, revised international staging system.

^a Teclistamab and elranatamab.

^b Talquetamab.

^c Including IMiDs, proteasome inhibitors, anti-CD38 monoclonal antibody, anti-PD1 monoclonal antibody and gamma-secretase inhibitor.

whereas GPRC5D-targeting BsAb and anti-bacterial prophylaxis were associated with a lower risk (HR = 0.53; 95% CI, 0.3–0.94 and HR = 0.65; 95% CI, 0.46–0.9, respectively, Fig. 2[C]). Gammaglobulinaemia >400 mg/dL and immunoglobulin substitution were not associated with a significantly lower risk (HR = 1.05; 95% CI, 0.67–1.64 and HR = 0.78; 95% CI, 0.52–1.17, respectively). In a post hoc multivariate model adjusted on bacterial prophylaxis, corticosteroid for CRS/ICANS and BsAb type, only the administration of corticosteroid for CRS/ICANS was correlated with a higher risk of first infection (HR = 2.01; 95% CI, 1.27–3.19).

Finally, focusing only on grade ≥3 infections, corticosteroids for CRS/ICANS were associated in a univariate analysis with Fine and Gray models with death before the first infection as a competing risk event with a higher risk of infection (HR = 2.02; 95% CI, 1.32–3.09; p 0.01), whereas GPRC5D-targeting BsAb (HR = 0.54; 95% CI, 0.31–0.94; p 0.02), and anti-bacterial prophylaxis (HR = 0.66; 95% CI, 0.47–0.92; p 0.01) were associated with a lower risk. In a multivariate model adjusted on bacterial prophylaxis, corticosteroid for CRS/ICANS and BsAb type, only the administration of corticosteroid for CRS/ICANS was correlated with a higher risk of first grade ≥3 infections (HR = 1.88; 95% CI, 1.2–2.95; p 0.006).

Discussion

In this large-scale real-world multicentre study we found a global cumulative incidence of first infections impacting patient management of 70%. Among the 234 infection events recorded, 53% were grade ≥3, 44% induced a modification of the haematologic treatment, and 9% resulted in death. The infection rate was lower in GPRC5D-targeted BsAb (51%) when compared with anti-BCMA agents (73%). Only the use of corticosteroids for CRS/ICANS was independently associated with the occurrence of a first infection affecting patient management.

The risk of acquiring infections in patients with BsAb-treated MM is multifactorial. First, MM is associated with B-cell

depletion, hypogammaglobulinaemia, and T-cell dysfunction [19]. Second, almost all patients who received BsAb had already been treated with many prior lines of therapy, thereby increasing their susceptibility to infections. Third, BsAb-targeted therapy is associated with significant neutropaenia, lymphopaenia, T-cell exhaustion and hypogammaglobulinaemia [5], directly increasing the risk of acquiring infections, but also with the development of CRS, which is treated with immunosuppressive agents [9–12]. Our results are consistent with the high rates of infection observed in BsAb clinical trials [6,8,11,20]. In the phase I/II teclistamab MajesTEC-1 and the phase II elranatamab MagnetisMM-3 studies, 76.4% and 66.7% of patients experienced any grade infection, respectively [6,8]. In the MonumentAL-1 study with talquetamab, rates of infection were observed to be lower with 57.3% of patients receiving the 0.4 mg/kg dose experiencing any grade infections [7]. In a meta-analysis of clinical trials [9,12] the prevalence of all-grade infections was of 50% to 56% among patients with MM treated with BsAb, with no difference among patients treated on-trial with BCMA-targeting BsAb monotherapy and with non-BCMA-targeting BsAb monotherapy. However, grade ≥3 infections were significantly higher among BCMA-targeting BsAb compared with non-BCMA BsAb [9,12]. A recent worldwide pharmacovigilance study found a higher number of reported infections with BCMA-targeting than other BsAb [21]. Similarly, Hammons et al. [14] reported higher rates of infectious events under BCMA-targeting BsAb compared to monotherapy GPRC5D-targeting BsAb. Although the lack of statistical power due to the low number of patients treated with GPRC5D-targeting BsAb may have contributed to inconsistent results between the two multivariate analyses models we used, our data are in line with a higher incidence of infections when BCMA-targeting BsAb are used.

Preventive measures that aim to mitigate the risk of infection in patients with MM are of tremendous importance. Previous studies have shown that hypogammaglobulinaemia is associated with an increased risk of infections [13,22] and have underlined the protective effect of immunoglobulin supplementation [23].

Table 2
Characteristics and grades of infections impacting patient management

Variables	Total (n = 234)
Site of infection, n (%)	
Systemic	52 (22)
Upper respiratory tract	19 (8)
Lower respiratory tract	97 (41)
Gastrointestinal tract	23 (10)
Genitourinary tract	23 (10)
Skin and soft tissue	11 (5)
CNS	2 (1)
Pathogens isolated ^a , n (%)	n = 165
Bacterial	92/165 (56)
Enterobacteriaceae	48/165 (29)
<i>Pseudomonas aeruginosa</i> and other non-fermentative gram-negative bacteria	13/165 (7)
Anaerobic bacteria	11/165 (6)
Enterococci	6/165 (4)
Staphylococci	5/165 (3)
Streptococci ^b	4/165 (2)
<i>Haemophilus influenzae</i>	4/165 (2)
<i>Neisseria</i>	1/165 (1)
Viral	63/165 (38)
Respiratory viruses ^c	40/165 (24)
CMV	8/165 (5)
Enterovirus	3/165 (2)
HSV	2/165 (1)
VZV	2/165 (1)
Parvovirus B19	2/165 (1)
HBV	2/165 (1)
JC virus	2/165 (1)
Sapovirus	1/165 (1)
Adenovirus	1/165 (1)
Fungi	8/165 (5)
<i>Aspergillus spp</i>	6/165 (4)
<i>Scedosporium spp</i>	1/165 (1)
<i>Pneumocystis jirovecii</i>	1/165 (1)
Parasites	2/165 (1)
Toxoplasmosis	1/165 (1)
Giardiasis	1/165 (1)
Undocumented	69 (29)
Grade of infection ^d , n (%)	
1	12/234 (5)
2	98/234 (41)
3	75/234 (32)
4	28/234 (12)
5	20/234 (9)

CMV, cytomegalovirus; CNS, central nervous system; HBV, hepatitis B virus; HSV, herpes simplex virus; VZV, varicella zoster virus.

^a From 159 MDI of which 6 were co-infections.

^b Including *S. pneumoniae*.

^c Including SARS-CoV-2 (n = 21), influenza/parainfluenza viruses (n = 14), rhinovirus (n = 2), respiratory syncytial virus (n = 2) and metapneumovirus (n = 1).

^d n = 1 missing data.

Although hypogammaglobulinaemia and immunoglobulin substitution did not reach statistical significance in our study, the high frequency of bacterial respiratory infections supports immunoglobulin supplementation in BsAb-treated patients with severe hypogammaglobulinaemia or repeated infections [20,24]. In the same line, patients should receive yearly *Influenza* vaccination, updated SARS-CoV-2 vaccination, pneumococcal vaccination, and recombinant varicella zoster vaccination [20,25]. The benefit of the recently available RSV (respiratory syncytial virus) vaccines will have to be considered [26]. Recent guidelines recommend universal anti-herpes simplex virus/varicella zoster virus and anti-*Pneumocystis* prophylaxis in BsAb-treated patients with MM, but not routine prophylaxis against cytomegalovirus (CMV) [20,24]. Given that CMV infection was not exceptional in

our study, biological monitoring of CMV DNAemia has to be considered. These guidelines also recommend fluconazole prophylaxis in case of a history of fungal infection, prolonged neutropaenia or steroid administration [20,24]. Given that prolonged neutropaenia was rare, dexamethasone therapy was rarely continued after step-up doses, and fungal infections were mainly caused by moulds, we would instead advocate for the use of a prophylaxis active against moulds in case of an important risk of fungal infection. Conversely, general anti-bacterial prophylaxis is not recommended except in case of prolonged neutropaenia or history of recurrent bacterial infections [20,24]. Given the high frequency of bacterial infections in our study, anti-bacterial prophylaxis may be discussed in high-risk patients. Furthermore, we found that the use of corticosteroids to manage CRS or ICANS was independently associated with the risk of infection. Indeed, while the frequency of CRS/ICANS was similar, none of the GPRC5D-targeting BsAb-treated patients received corticosteroids, although they received tocilizumab more frequently. Although the risk of infections was not increased using corticosteroids for CRS/ICANS in patients treated with anti-BCMA CAR T-cells, corticosteroids have been reported as a risk factor in patients with MM treated in combination with PIs, IMiDs or monoclonal Abs [27]. Altogether this suggests that corticosteroids might contribute to infections in BCMA-targeting BsAb-treated patients, advocating for their cautious use in this setting, in line with recent guidelines [24]. Finally, one study suggests that a limited duration of BsAb treatment with extended treatment-free intervals may result in lower risks of complications without impairing the outcome [28].

To our knowledge, this is the first large-scale real-world multi-centre series of BsAb-treated patients reported to date. This nationwide retrospective study provides insights into the epidemiology and characteristics of infections associated with MM BsAb treatment. In our data analysis, we performed a Fine and Gray model to account for the competing risk of death occurring before infectious events. Non-competing risk statistical models used in previous studies [11,13,21,23] may have overestimated the risk [29]. This is the first study to use a competing risk analysis allowing a more accurate estimation of the infectious risk in patients treated with BsAb. To compare our results with previous studies using Cox models, we performed a second analysis with a Cox model and obtained similar results. However, this study is limited by its retrospective nature and the heterogeneity of infections, prophylactic treatment and BsAb. In particular, there were few patients treated with GPRC5D-targeting BsAb. Data were insufficient to analyse other biological risk factors, such as neutropaenia and lymphopaenia. The CRS occurring with the first cycle of BsAb might have been mistaken as infections and considered as FUF; however, this would have concerned only three patients. Although there was no control group in our study, a descriptive study detailing the use of real-life standard of care in RR-MM patients not receiving BsAb revealed an infection rate of 28.6%, including 6.5% of grade 3 to 4 events [30]. Finally, our study was limited to infections affecting patient management which may have led to overestimate the severity of infectious events. Despite these limitations, our data provide physicians with useful insights into infectious complications under BsAb therapy that may help improve the strategies for prevention and treatment of infections.

To conclude, BsAb are associated with frequent infections that affect patients' therapeutic management. Implementation of preventive measures that aim to mitigate the risk of infection in BsAb-treated patients with MM is pivotal, particularly in patients who received corticosteroids for CRS/ICANS. A rational use of corticosteroids in the management of CRS or ICANS is advised.

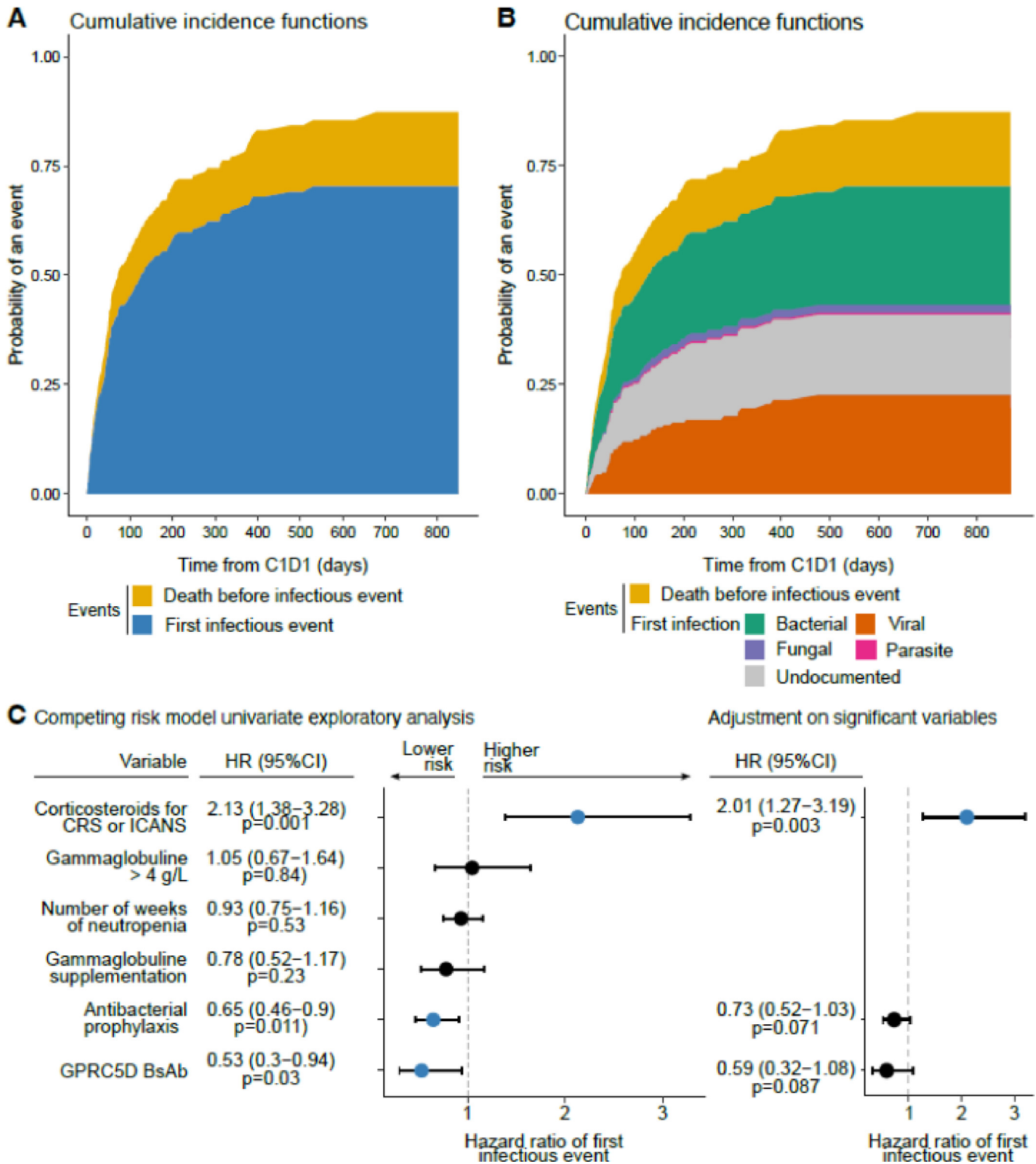


Fig. 2. Cumulative incidence of first infection. (A) Cumulative incidence function (CIF) of first infection. Death before first infection was used as a competing risk event. (B) The CIF of the first infection according to pathogen. Death was also used as a competing risk event. (C) Forest plot summarizing competing risk univariate exploratory analysis and multivariate adjustment of variables associated with first infection with death defined as a competing risk. Fine and Gray models were used to compute hazard ratios (HR), 95% CI and p-values.

Author contributions

The authors confirm contribution to the paper as follows: Study conception and design: TC, AP, and GMB; Data collection: EC, AJ, SH, GE, EF, FD, CS, SS, CC, CDD, XB, PB, AC, MC, AR, VR, and TC; Data curation: EC, AJ, and NV; Analysis methods and materials: NV;

Interpretation of results: NV, TC, AP, GMB, EC, and AJ; Figures generation: NV; Draft manuscript preparation: EC and AJ. All authors reviewed the results and approved the final version of the manuscript. EC and AJ contributed equally to the paper's contents and can consider themselves co-first authors on their CVs. Authors EC, AJ, TC, NV and AP contributed equally to the work.

Transparency declaration

The authors have no conflicts of interest to declare.

Financial report

The authors received no financial support for the research, authorship, or publication of this article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.cmi.2024.02.023>.

References

- [1] Cowan AJ, Allen C, Barac A, Basaleem H, Bensenor I, Curado MP, et al. Global burden of multiple myeloma: a systematic analysis for the global burden of disease study 2016. *JAMA Oncol* 2018;4:1221–7. <https://doi:10.1001/jamaoncol.2018.2128/>.
- [2] Avet-Loiseau H. Ultra high-risk myeloma. *Hematol Am Soc Hematol Educ Program* 2010;2010:489–93. <https://doi:10.1182/asheducation-2010.1.489>.
- [3] Brinkmann U, Kontermann RE. Bispecific antibodies. *Science* 2021;372:916–7. <https://doi:10.1126/science.abg1209>.
- [4] Longhitano AP, Slavin MA, Harrison SJ, The BW. Bispecific antibody therapy, its use and risks for infection: bridging the knowledge gap. *Blood Rev* 2021;49:100810. <https://doi:10.1016/j.blre.2021.100810>.
- [5] Swan D, Routledge D, Harrison S. The evolving status of immunotherapies in multiple myeloma: the future role of bispecific antibodies. *Br J Haematol* 2022;196:488–506. <https://doi:10.1111/bjh.17805>.
- [6] Moreau P, Garfall AL, van de Donk NWCJ, Nahii H, San-Miguel JF, Oriol A, et al. Teclistamab in relapsed or refractory multiple myeloma. *N Engl J Med* 2022;387:495–505. <https://doi:10.1056/NEJMoa2203478/>.
- [7] Chari A, Minnema MC, Berdeja JG, Oriol A, van de Donk NWCJ, Rodriguez-Otero P, et al. Talquetamab, a T-cell-redirecting GPRC5D bispecific antibody for multiple myeloma. *N Engl J Med* 2022;387:2232–44. <https://doi:10.1056/NEJMoa2204591/>.
- [8] Lesokhin AM, Tomasson MH, Arnulf B, Bahlis NJ, Miles Prince H, Niesvizky R, et al. Elranatamab in relapsed or refractory multiple myeloma: phase 2 MagnetisMM-3 trial results. *Nat Med* 2023;29:2259–67. <https://doi:10.1038/s41591-023-02528-9>.
- [9] Mazahreh F, Mazahreh L, Schinke C, Thanendrarajan S, Zangari M, Shaughnessy JD, et al. Risk of infections associated with the use of bispecific antibodies in multiple myeloma: a pooled analysis. *Blood Adv* 2023;7:3069–74. <https://doi:10.1182/bloodadvances.2022009435>.
- [10] Mohan M, Nagavally S, Dhakal B, Radhakrishnan SV, Chhabra S, D'Souza A, et al. Risk of infections with B-cell maturation antigen-directed immunotherapy in multiple myeloma. *Blood Adv* 2022;6:2466–70. <https://doi:10.1182/bloodadvances.2021006178>.
- [11] Sim BZ, Longhitano A, Er J, Harrison SJ, Slavin MA, Teh BW. Infectious complications of bispecific antibody therapy in patients with multiple myeloma. *Blood Cancer J* 2023;13:34. <https://doi:10.1038/s41408-023-00808-8>.
- [12] Reynolds G, Cliff ERS, Mohyuddin GR, Popat R, Midha S, Ng Liet Hing M, et al. Infections following bispecific antibodies in myeloma: a systematic review and meta-analysis. *Blood Adv* 2023;7:5898–903. <https://doi:10.1182/bloodadvances.2023010539>.
- [13] Lancman G, Parsa K, Rodriguez C, Richter J, Cho HJ, Parekh S, et al. Infections and severe hypogammaglobulinemia in multiple myeloma patients treated with anti-BCMA bispecific antibodies. *Blood* 2022;140:10073–4. <https://doi:10.1182/blood-2022-163733>.
- [14] Hammons LR, Szabo A, Janardan A, Bhatlapenumarthi V, Annyapu E, Dhakal B, et al. The changing spectrum of infection with BCMA and GPRC5D targeting bispecific antibody (bsAb) therapy in patients with relapsed refractory multiple myeloma. *Haematologica* 2024;109:906–14. <https://doi:10.3324/haematol.2023.283590>.
- [15] From the Immunocompromised Host Society. The design, analysis, and reporting of clinical trials on the empirical antibiotic management of the neutropenic patient. Report of a consensus panel. *J Infect Dis* 1990;161:397–401. <https://doi:10.1093/infdis/161.3.397>.
- [16] US Department of Health and Human Services. Common terminology criteria for adverse events v5.0. 2017.
- [17] Lee DW, Santomaso BD, Locke FL, Ghobadi A, Turtle CJ, Brudno JN, et al. ASTCT Consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. *Biol Blood Marrow Transplant* 2019;25:625–38. <https://doi:10.1016/j.bbmt.2018.12.758>.
- [18] Vallet N, Michonneau D, Tournier S. Toward practical transparent verifiable and long-term reproducible research using Guix. *Sci Data* 2022;9:597. <https://doi:10.1038/s41597-022-01720-9>.
- [19] Murakami H, Ogawara H, Hiroshi H. Th1/Th2 cells in patients with multiple myeloma. *Hematology* 2004;9:41–5. <https://doi:10.1080/1024533031001652437>.
- [20] Raje N, Anderson K, Einsele H, Efebera Y, Gay F, Hammond SP, et al. Monitoring, prophylaxis, and treatment of infections in patients with MM receiving bispecific antibody therapy: consensus recommendations from an expert panel. *Blood Cancer J* 2023;13:116. <https://doi:10.1038/s41408-023-00879-7>.
- [21] Contejean A, Janssen C, Orsini-Piocelle F, Zecchini C, Charlier C, Chouchana L. Increased risk of infection reporting with anti-BCMA bispecific monoclonal antibodies in multiple myeloma: a worldwide pharmacovigilance study. *Am J Hematol* 2023;98:E349–53. <https://doi:10.1002/ajh.27071>.
- [22] Hammons LR, Szabo A, Janardan A, Dhakal B, Chhabra S, D'Souza A, et al. Kinetics of humoral immunodeficiency with bispecific antibody therapy in relapsed refractory multiple myeloma. *JAMA Netw Open* 2022;5:e2238961. <https://doi:10.1001/jamanetworkopen.2022.38961>.
- [23] Lancman G, Parsa K, Kotlarz K, Avery L, Lurie A, Liberman-Cribbin A, et al. IVIg use associated with ten-fold reduction of serious infections in multiple myeloma patients treated with anti-BCMA bispecific antibodies. *Blood Cancer Discov* 2023;4:440–51. <https://doi:10.1158/2643-3230.BCD-23-0049>.
- [24] Ludwig H, Terpos E, van de Donk N, Mateos MV, Moreau P, Dimopoulos MPA, et al. Prevention and management of adverse events during treatment with bispecific antibodies and CAR T cells in multiple myeloma: a consensus report of the European Myeloma Network. *Lancet Oncol* 2023;24:e255–69. [https://doi:10.1016/S1470-2045\(23\)00159-6](https://doi:10.1016/S1470-2045(23)00159-6).
- [25] Anderson TC, Masters NB, Guo A, Shepersky L, Leidner AJ, Lee GM, et al. Use of recombinant zoster vaccine in immunocompromised adults aged ≥19 years: recommendations of the advisory committee on immunization practices – United States, 2022. *MMWR Morb Mortal Wkly Rep* 2022;71:80–4. <https://doi:10.15585/mmwr.mm7103a2>.
- [26] Melgar M, Britton A, Roper LE, Keipp Talbot H, Long SS, Kotton CN, et al. Use of respiratory syncytial virus vaccines in older adults: recommendations of the advisory committee on immunization practices – United States, 2023. *MMWR Morb Mortal Wkly Rep* 2023;72:793–801. <https://doi:10.15585/mmwr.mm7229a4>.
- [27] Lim C, Sinha P, Harrison SJ, Quach H, Slavin MA, Teh BW. Epidemiology and risks of infections in patients with multiple myeloma managed with new generation therapies. *Clin Lymphoma Myeloma Leuk* 2021;21:444–450.e3.
- [28] Philipp N, Kazerani M, Nicholls A, Vick B, Wulf J, Straub T, et al. T-cell exhaustion induced by continuous bispecific molecule exposure is ameliorated by treatment-free intervals. *Blood* 2022;140:1104–18. <https://doi:10.1182/blood.2022015956>.
- [29] Schuster NA, Hoogendijk EO, Kok AAL, Twisk JWR, Heymans MW. Ignoring competing events in the analysis of survival data may lead to biased results: a nonmathematical illustration of competing risk analysis. *J Clin Epidemiol* 2020;122:42–8. <https://doi:10.1016/j.jclinepi.2020.03.004>.
- [30] Mateos MV, Weisel K, De Stefano V, Goldschmidt H, Delforge M, Mohty M, et al. LocoMMotion: a prospective, non-interventional, multinational study of real-life current standards of care in patients with relapsed and/or refractory multiple myeloma. *Leukemia* 2022;36:1371–6. <https://doi:10.1038/s41375-022-01531-2>.