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par

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TITRE

Caractéristiques et incidence des infections impactant la prise en charge des patients avec un myélome multiple traités par anticorps bispécifiques, une étude rétrospective nationale réalisée avec l'Intergroupe Francophone du Myélome et le G2i.

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RESUME EN FRANÇAIS :

Introduction : Les anticorps bispécifiques (AcBs) sont des nouvelles immunothérapies efficaces chez les patients avec un myélome multiple en rechute ou réfractaire (MMRR). Cependant, les complications infectieuses sont fréquentes principalement chez les patients traités avec des AcBs ciblant le BCMA. Cette étude a pour objectif de décrire les caractéristiques des infections impactant la prise en charge des patients et de décrire l'incidence cumulative de la première infection ainsi que les variables associées à ce risque.

Méthode : Nous avons mené une étude rétrospective sur 14 centres français de l'Intergroupe Francophone du Myélome incluant tous les patients traités par AcBs anti-BCMA ou anti-GPRC5D entre décembre 2020 et février 2023. Nos objectifs étaient de décrire les caractéristiques et incidence des infections impactant la prise en charge des patients traités par anticorps anti-BCMA ou anti-GPRC5D et de rechercher les facteurs de risques associés.

Résultats : Parmi les 229 patients inclus, 200 (87 %) étaient traités par un AcBs anti-BCMA, dont 153 par Teclistamab et 47 avec l'Elranatamab et 29 patients (13 %) par l'AcBs anti-GPRC5D, le Talquetamab. L'âge médian était de 67 ans, le nombre médian de lignes antérieures était 4 et 82 % des patients étaient triple-réfractaires. Les taux de CRS et ICANS tout grade étaient similaires dans les 2 groupes (60 à 66% et 5 à 7% respectivement). Aucun des patients du groupe traité par anti-GPRC5D n'a reçu de corticoïdes pour la gestion d'un CRS ou ICANS (contre 19 % chez les patients traités par anti-BCMA) mais l'utilisation du Tocilizumab était plus fréquente (41 % contre 23 %). Durant la période de l'étude, nous rapportons 234 événements infectieux. Cent quarante-deux patients (62%) ont présenté au moins un évènement infectieux avec une durée médiane avant la première infection de 49 jours. Les infections de grade ≥ 3 représentaient 53 % des infections dont 9 % de grade 5. Toutes les infections de grade 4 et 5 ont eu lieu chez des patients sous anti-BCMA. Une majorité des infections étaient d'origine respiratoire (50 % ; n=116) ou disséminée (22 % ; n=52). Parmi les infections documentées, 56 % étaient bactériennes (n=92), 38 % virales (n=63) et 5% d'origine fongique (n=8) avec également 2 cas de parasitose. Les pathogènes les plus fréquents étaient les *Enterobacteriaceae* (n=48, 29 %), Sars-Cov2 (n=21, 13 %) et les bactéries anaérobies (n=11, 6%). Nous rapportons 6 cas d'aspergillose pulmonaire invasive, 2 cas de JC virus et une toxoplasmose disséminée.

L'incidence cumulative de première infection dans la population totale était de 70%, 73% chez les patients traités par AcBs ciblant le BCMA et 51% pour ceux ciblant le GPRC5D. Dans l'analyse univariée, l'utilisation des corticostéroïdes pour la gestion des CRS/ ICANS était associée à une augmentation du risque de la première infection (HR =2.13; 95% CI, 1.38-3.28), tandis que les AcBs ciblant le GPRC5D et l'antibioprophylaxie étaient associés à une réduction du risque de première infection (HR = 0.53; 95% CI, 0.3-0.94 and HR = 0.65; 95% CI, 0.46-0.9). Le modèle multivarié de Fine et Gray a montré que seule l'utilisation de corticostéroïdes pour la gestion d'un CRS ou ICANS était associée à une augmentation du risque de première infection (HR = 2.01; 95% CI, 1.27-3.19). L'analyse centrée sur les premières infections de grade ≥ 3 a mis en évidence des résultats identiques.

Conclusion : Les résultats de cette étude soulignent la forte proportion d'infections dont plus de la moitié sont de grade ≥ 3 chez les patients traités par AcBs. Ces données renforcent l'importance des prophylaxies anti-virales et anti-pneumocystose, ainsi que l'ajout d'une antibioprophylaxie et encouragent une utilisation précautionneuse des corticoïdes dans cette population.

Characteristics and incidence of infections in patients with multiple myeloma treated by bispecific antibodies: a national retrospective study on the behalf of G2I and Intergroupe Francophone du Myelome

Abstract

Background. Bispecific antibodies (BsAb) are a new effective treatment for relapsed/refractory multiple myeloma (RRMM). Although these immunotherapies are well tolerated, infectious complications emerged as a predominant issue, mainly with anti-BCMA BsAb. In this study, we aimed to describe characteristics of infections affecting the management of patients treated with BCMA-targeting or GPRC5D-targeting BsAb and identify their risk factors.

Methods. A retrospective study was conducted in 14 tertiary centers including patients treated by BsAb between December 2020 and February 2023. Our objectives were to describe characteristics of infections affecting the management of patients treated with BCMA-targeting or GPRC5D-targeting BsAb and identify their risk factors.

Results. Among the 229 patients included, 200 (87%) received a BCMA-targeting BsAb with Teclistamab (n=153, 67%) or Elranatamab (n=47, 20%) and 29 patients (13%) received a GPRC5D-targeting BsAb with Talquetamab. The median age was 67 years, median of prior line of therapy was 4 and 82% of patients were triple refractory. CRS and ICANS rate were similar in both group (60-66% and 5-7% respectively). None of the patients treated with GPRC5D BsAb received corticosteroids for CRS or ICANS (versus 19% in BCMA-targeting BsAb treated patients) although the use of Tocilizumab was more frequent (41% vs 23%). With a median follow up of 7 months (IQR 4-12 months), 234 infectious events were documented in 142 patients (62%) with a median time to the first infection of 49 days. Fifty three percent of infections were grade ≥ 3 including 9% of grade 5. All infections grade ≥ 4 (n= 48; 20.6%) occurred in patients treated with anti-BCMA BsAb. Predominant localisation was pulmonary tract (n= 116, 50%) and disseminated infection (n=52, 22%). Among the documented infections, 92 (56%) were bacterial, 63 (38%) were viral and 8 (5%) were fungal. Two (1.2%) infectious events were from a parasite. Most frequent pathogens were *Enterobacteriaceae* (n=48, 29%), SARS-CoV-2 (n=21, 13%) and anaerobic bacteria (n=11, 6%). We also report 6 cases of invasive pulmonary aspergillosis, 2 cases of JC virus and 1 disseminated toxoplasmosis.

Global cumulative incidence of the first infection was 70% in all patients, 73% in patients treated with BCMA-targeting, and 51% with GPRC5D-targeting BsAb. In univariate analyses, corticosteroids for CRS/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). Analysis focusing on grade ≥ 3 first infections revealed identical results.

Conclusion. This study highlights the rate of infectious event with BsAb treatment, with more than half of them grade ≥ 3. 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.

Mots clés:

Myélome multiple
Immunothérapie
Anticorps bispécifique
Infections
Facteurs de risque

Key words:

Multiple myeloma
Immunotherapy
Bispecific antibodies
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Risk factors

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En présence des enseignants et enseignantes
de cette Faculté,
de mes chers condisciples
et selon la tradition d'Hippocrate,
je promets et je jure d'être fidèle aux lois de l'honneur
et de la probité dans l'exercice de la Médecine.

Je donnerai mes soins gratuits aux indigents,
et n'exigerai jamais un salaire au-dessus de mon travail.

Admis(e) dans l'intérieur des maisons, mes yeux
ne verront pas ce qui s'y passe, ma langue taira
les secrets qui me seront confiés et mon état ne servira pas
à corrompre les mœurs ni à favoriser le crime.

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je rendrai à leurs enfants
l'instruction que j'ai reçue de leurs parents.

Que les hommes et les femmes m'accordent leur estime
si je suis fidèle à mes promesses.
Que je sois couvert(e) d'opprobre
et méprisé(e) de mes confrères et consœurs
si j'y manque.

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Sommaire

Abréviations:

ACST : Autologous stem cell transplantation
BCMA : B-cell maturation antigen
BsAb : bispecific antibody
CAR : Chimeric antigen receptor
CDI : Clinically defined infection
CR : Complete response
CH : Constant heavy chain
CL : Constant light chain
CRS : Cytokine release syndrome
Fab : Fragment antigen binding
Fc : Fragment crystallizable
FUF : Fever of unknown focus
G2i : Groupe Infection et Immunodepression network
GPRC5D : G protein–coupled receptor of family C, group 5, member D
HGG : Hypogammaglobulinemia
ICANS : Immune effector cell associated neurotoxicity syndrome
IFM : Intergroupe Francophone du Myélome
IMID : Immunomodulatory drugs
IMWG : International myeloma working group
IvIg : Intravenous immunoglobulin
mAb : Monoclonal antibody
MDI : Microbiologically defined infection
MM : Multiple myeloma
mPFS : Median progression free survival
m : months
OS : Overall survival
ORR : Overall response rate
PI : Proteasome inhibitors
PJP : Pneumocystis jirovecii
RR : Relapse or refractory
ScFv : Single chain variable fragment
TAA : Tumor associated antigen
TCE : T-cell engager
TL : T lymphocyte
VH : Variable heavy chain
VL : Variable light chain

Characteristics and incidence of infections in patients with multiple myeloma treated by bispecific antibodies: a national retrospective study on the behalf of G2I and IFM

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I. Introduction

A. Multiple Myeloma

1. Definition and epidemiology

Multiple myeloma (MM) is a clonal proliferation of plasma cells in the bone marrow usually accompanied by a secretion of monoclonal immunoglobulin. It accounts for 1% of all cancers and 10% of hematological malignancies and is therefore the most frequent in France with 6487 new cases in 2023. MM affects preferentially men with a sex ratio of 1.2 and the median age is about 72 years old[1]. Patients are eligible for treatment when their disease is symptomatic, including renal failure, anemia, hypercalcemia or osteolytic bone lesions referred to as CRAB criterias. They are also eligible in the presence of high-risk biomarker, the SLiM criterias, including >60% of bone marrow invasion, high serum free light chain ratio (>100) or >1 lesion detected on MRI[2].

2. Treatments

Before 2015, the treatment of multiple myeloma was based on the association of immunomodulatory drugs or IMID with lenalidomide (R) and thalidomide (T), proteasome inhibitors or PI with bortezomib (V) and dexamethasone (d). The prognosis of MM patients has been greatly improved by the advent of immunotherapy with anti-CD38 monoclonal antibodies (mAb), initially daratumumab (D). The addition of daratumumab to the combination of VTd in transplant-eligible patients in the CASSIOPEA study showed a superior rate of stringent complete response in the D-VTd arm (29% vs 20%, OR 1.60, p=0.001)[3]. The PERSEUS study confirmed the major contribution of the anti-CD38 mAb to enhance patient's prognosis, showing a PFS (progression free survival) of 84.3% at 4 years in the D-VRd group compared to 67.7% in the VRd group (HR = 0.42, p<0.001)[4]. These results have established a new standard of care in this population. Patients receive 4 to 6 cycles of the quadruplet described above, followed by an intensification with high-dose melphalan chemotherapy and autologous stem cell transplantation (ACST). The consolidation phase consists of 2 to 4 cycles of the four prior drugs and precedes a 3-years maintenance period with lenalidomide.

Elderly and unfit patients are not eligible for ACST but also benefit from the addition of an anti-CD38 mAb. The MAIA study established DRd as the standard of care for initial therapy. At 4.5 years, a superior median PFS (mPFS) was observed in the DRd group, as it was not yet reached (57% without progressive disease), compared to 34.4 months in the Rd arm (41%) (HR= 0.53 , p<0.0001)[5]. Isatuximab is a more recent anti-CD38 with similar efficacy to Daratumumab[6]. Results from the CEPHEUS and BENEFIT studies, demonstrated an improved response with the addition of a proteasome inhibitor, bortezomib (V), and confirmed its safety in this population[7]. However, it should still be avoided in the frailest patients due to the increased risk of neutropenia and neuropathy. This treatment should be continued until progression or intolerance in these patients[5,7].

Despite impressive response rates and prolonged remissions achieved with initial treatment, the majority of patients relapse. The new generation of PIs and IMIDs has allowed advances in the management of these patients. Carfilzomib (K) in combination with dexamethasone doubled the median PFS achieved with Vd in the ENDEAVOR study (18.7m vs 9.4, HR= 0.53, p<0.0001)[8]. Similarly, the addition of pomalidomide to Vd improved the PFS (11m vs 7m, HR 0·61, p<0·0001)[9]. These improvements were further enhanced by the addition of anti-CD38 mAb. Daratumumab in combination with Kd or Pd in the CANDOR and APOLLO trials nearly doubled the mPFS from 15.2m to 28.6m with DKd and from 6.9 to

12.4m with DPd[10,11]. Isatuximab is also efficient in this setting especially in combination with Kd in the IKEMA study revealing a mPFS of 35.7m in the IKd arm compared to 19.2m for Kd (HR 0.58)[12]. Nevertheless, the duration of response in this setting was still short and patients eventually relapsed developing resistance to these therapies. The prognostic of relapse or refractory (RR) patients is dismal. In the MAMMOTH study, anti-CD38 mAb refractory patients had a median overall survival (OS) of 8,6m and a next line response rate of only 31%[13]. Patients exposed to an IMID, PI and anti-CD38 mAb, referred to as triple class exposed patients, showed a mPFS and OS of 4,6 and 12,4 months respectively in the prospective real-life care study, LocoMMotion[14]. These patients therefore represented a new therapeutic challenge.

3. Novel immunotherapies

Elimination of abnormal cells by the immune system is defective in tumors. Cancer cells corrupt the immune system, among which T lymphocytes (TL), to allow tumor growth. Furthermore, iterative treatment and constant exposition to tumor antigen leads to TLs exhaustion and their inability to eliminate tumor cells[15,16]. In this context emerged novel immunotherapies aiming to redirect T-cell cytotoxicity against cancer cells. Chimeric antigen receptor T-cells (CAR-T) are patient's own T-cells, modified to express a fragment of an immunoglobulin directed against cancer cells. In MM, the two main CAR-T cells, idecabtagene vicleucel and ciltacabtagene autoleucel, have shown remarkable efficacy in the triple refractory population with a mPFS of 13.3m and 35m respectively[17,18]. Another promising strategy using TLs is rising, bispecific antibodies.

B. Bispecific antibodies

1. Structure and mechanism of action

Bispecific antibodies are artificial antibodies able to simultaneously bind two different antigens. Several structures exist but they most commonly are IgG-like with two halves of different mAb composed of a heavy chain with 3 constant domains (CH1-3), a variable one (VH) and a light chain with one variable (VL) and constant domain (CL)[19]. The VH and VL form a variable fragment specific for an antigen *(Figure 1A*). BsAbs called T-cell engagers (TCE) are directed against a tumor associated antigen (TAA) on tumor cells and the CD3 TCR's subunit. The simultaneous binding of the two targets forms an immunological synapse. Interaction with the CD3 induces T cell activation independently of TCR/CMH recognition and

costimulatory signals. T cell activation results in the release of cytokines (TNFa, INFy, interleukins) inducing T cell proliferation and the secretion of cytotoxic factors (B-granzyme and perforin) leading to tumor cell death [20,21](*Figure 1B*).

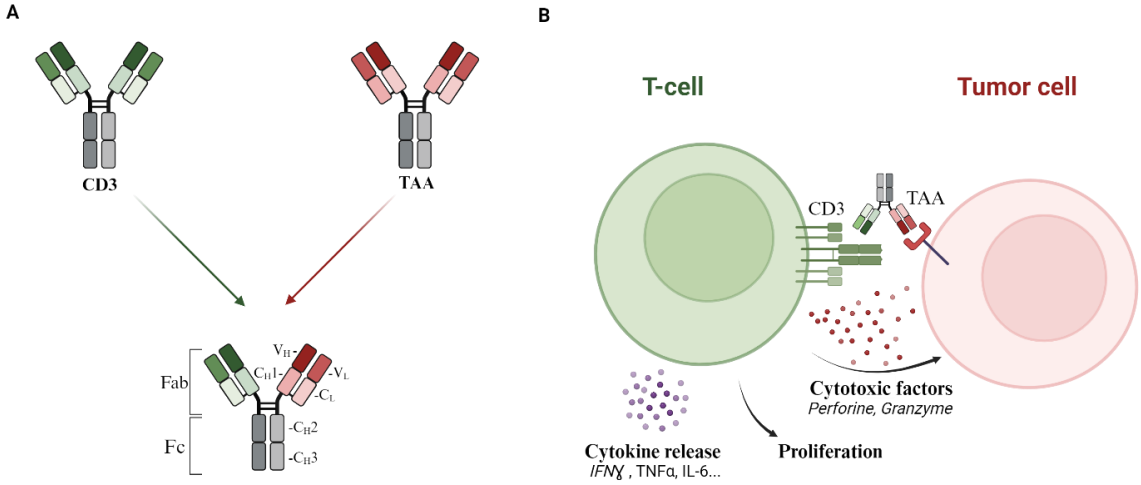

Figure 1. Structure and BsAb mechanism of action. (A) Example of an IgG-like BsAb with two different heavy and light chains. The antigen binding fragment (Fab) is composed of the light chain's constant and variable regions (CL and VL) and the variable and first constant domain of the heavy chain (VH and CH1). Constant domains CH-2 and 3 form the constant fragment (Fc). **(B)** Immunological synapse formed by the BsAb directed against CD3 and a TAA. The TL, activated by the interaction between the BsAb and CD3, releases cytotoxic factors inducing tumor cell death and pro-inflammatory cytokines allowing for the proliferation and recruitment of other immune cells at the tumor site, *adapted from Stephanie Harel et al, Revue Immunité et Cancer, 2024*.

2. BsAb's development and evolution

The development of BsAbs started in the 1950's with the work of R. Porter who succeeded in splitting an IgG mAb into several fragments via an enzyme called papaïne. One of the resulting fragments could be crystallized (Fc fragment) and did not recognize the antigen whereas the other two (fragment I and II) were able to do so[22,23]. Fragments I and II were then called Fab for fragment antigen binding. In 1964, Nisonoff first published the first BsAb's design by enzymatic cleavage of mAbs and chemical binding of two different Fabs, creating a molecule then called hybrid antibody with dual specificity[24]. In the following years, it was demonstrated that targeting the T-cell receptor with a mAb coupled to any cell surface could induce T-cell activation and proliferation therefore inducing T-cell specific lysis, bypassing TCR recognition[25]. This knowledge led U. Staerz and D. Segal in 1985 to develop BsAbs directed against tumor cells and T-cells via CD3, which could focus effector T-cell activity against tumor cells[26,27]. At this period, BsAbs were produced by hybrid hybridoma fusioning

two hybridoma producing mAb or by a chemical technique creating covalent bonds, the crosslinking technique. However, production difficulties considerably slowed their technological development until the end of the 1990s. The emergence of new technologies, especially molecular engineering allowed for the production of new immunoglobulin fragments, called Single chain variable fragment (ScFv), which only links the VH and VL by a spacer[28].

This led to the development of single-chain tandem Fv BsAbs connecting two distinct ScFv, (*Figure 2A)*. Blinatumomab, which targets CD19 on B-lymphocyte tumor cells and CD3 on T-cells, is a BsAb with this structure and the was first to receive FDA (Food drug and administration) approval for the treatment of a hematologic malignancy, acute lymphoblastic leukemia[29,30.] Despite its efficacy, single chain tandem Fv BsAb are small molecules and are rapidly eliminated by the organism and are therefore administered in a continuous manner. In order to overcome this difficulty and allow for spaced injections, an constant fragment was added to the construct[31] *(Figure 2B)* .

Nowadays, BsAbs are created via genetic engineering using bacteria or mammalian cells (Chinese hamster ovary; CHO) modified by the insertion of plasmids encoding for the BsAbs fragments[32]. This technique alone can induce mismatch dimerisation of the heavy chains and poor heavy chain/light chain coupling, resulting in inefficient constructs. Various strategies have been developed during the past two decades to improve this issue by creating diverse mutations in the heavy chain - knob into hole, duobody, hinge mutation technology - in order to generate a complementary interface favouring heterodimerization over homodimerization. The Cross mab technology exchanges the CH1 domains on the heavy chain with the CL domains on the light chain in only one of the two BsAb's arms. The configuration of the constant domains of this arm becomes unique and allow for a significant reduction in heavy chain/light chain mismatches[33].

Many different structures can be created by deleting or adding domains. For example, the addition of a tumor antigen binding domain improves the target's affinity[34], (*Figure 2C)*. More recently trispecific antibodies resulting from the incorporation of a third binding site to a different antigen enables multi-target strategies[35] (*Figure 2D).*

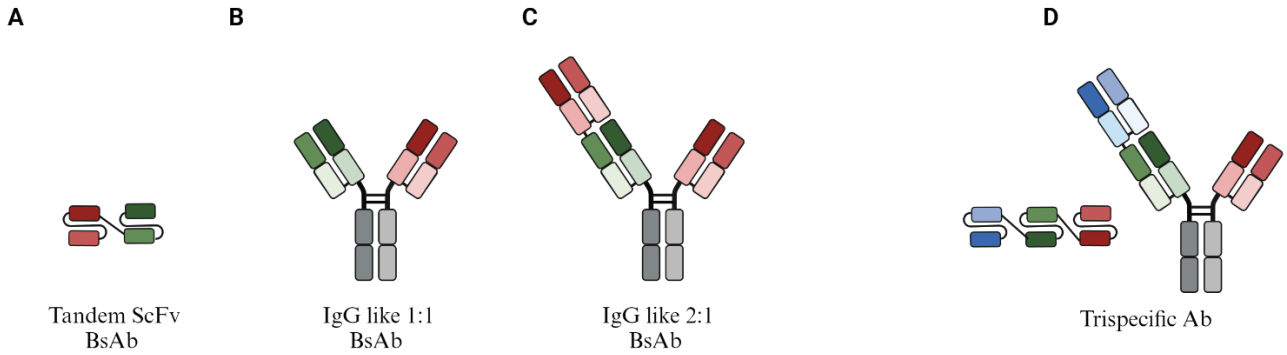

Figure 2. Example of bispecific and trispecific antibody constructs. (A) Tandem ScFv BsAb composed of two ScFv with one VL and one VH chain each, connected by a flexible linker. **(B)** IgG-like BsAb with the addition of an Fc fragment to improve its half-life and one binding site for each target (1:1). **(C)** IgG-like BsAb with 2 tumor binding sites (2:1). **(D)** Examples of trispecific antibodies with 3 ScFv or IgG-like.

3. BsAb's target in MM

The choice of the TAA targeted by the BsAb is important as it determines its tolerability and efficacy. The protein must be uniformly expressed on the tumor cell surface, but not on essential healthy tissues to prevent on-target off-tumor toxicities. In addition, target antigen loss or downregulation is a common resistance mechanism in cancer, the targeted antigen should therefore preferentially play a key role in tumor cell survival or proliferation[20]. BCMA and GPRC5D are the two main proteins targeted by BsAbs developed in MM.

B cell maturation antigen (BCMA) is a member of the tumor necrosis factor receptor superfamily that is expressed at high levels in both normal and malignant plasma cells, making it an ideal target antigen for MM therapies. By binding BCMA, multiple growth and survival signaling cascades are subsequently activated in the multiple myeloma (MM) cells, most frequently through NF-κβ, leading to the upregulation of anti-apoptotic proteins and production of cell adhesion molecules, angiogenesis factors, and immunosuppressive molecules. These leads to increased survival of MM cells[36–38].

G protein–coupled receptor of family C, group 5, member D (GPRC5D) is a novel target for MM immunotherapy. GPRC5D is highly expressed in MM cells but is also present in cells that produce hard keratin such as in hair follicles, nails and mucosa. Its physiological function and role in cancer remain unknown[39].

4. Main BsAbs in MM

The use of bispecific antibodies is currently limited to relapsed and refractory MM patients. However, trials are underway to assess their efficacy in earlier lines or in combination. Teclistamab and Elranatamab, two IgG-like 1:1 BsAbs targeting BCMA can be administered after 3 prior lines of therapy in triple class exposed patients. These BsAbs have demonstrated their efficacy in a heavily pre-treated population.

In the phase 1-2 MAJESTEC-1 study among triple class exposed patients, Teclistamab showed an overall response rate (ORR) of 63% with 39% of complete response (CR) and a 11.3 months mPFS, (*Table 1)*[40]. These impressive results have been confirmed by the RetrosTECtive study among 303 patients treated with Teclistamab in real world setting and found an ORR of 68% and mPFS of 11,3 months.

MagnetisMM-3 is a phase 2 study evaluating the efficacy of Elranatamab in a similar population. The ORR was of 61% with 35% CR and a mPFS of 17.3m[41], (Table 1).

Talquetamab is a GPRC5D-targeted BsAb evaluated in monotherapy in the phase 1-2 MonumenTAL-1 study. The ORR was 73% with 23% of CR and a mPFS of 12months at the highest concentration[42]. Marketing authorization (AMM: Autorisation de mise sur le marché) for this BsAb has not yet been granted, but some patients cant benefit from it in clinical trials.

Phase 3 studies are ongoing to evaluate these BsAbs, either as monotherapy or in combination, in comparison with associations of IP, IMiDs, and anti-CD38 mAbs[43,44,45].

	Teclistamab MajesTEC-1	Elranatamab MagnetisMM-3	Talquetamab MonumenTAL-1	
			0.04,g/kg	0.08,g/kg
Target	BCMA	BCMA	GPRC5D	
Patients, n	165	123	143	145
Median previous lines	5	5	6	6
Triple refractory patients, %	80	96.7	74	69
Overall response rate (ORR), %	63	61	74	73
mPFS,month	11.3	17.3	7.5	11.9
CRS, % (grade≥3,%) Median time to CRS, days Median duration, days	72.1 (0.6) 2 2	56 (0) 2 2	79 2 2	75 2 2
ICANS ,% (grade≥3, %)	3 (0)	3.4 (0)	11	11

Table 1. Main results from MajesTEC-1, MagnetisMM-3 and MonumenTAL-1 studies.

5. Toxicities management

a) CRS and ICANS

Activation of T-cells by BsAb results in an abundant secretion of pro-inflammatory cytokines such as IL-2, IL-6, IFN-γ, and TNF-α which can induce a systemic inflammatory response syndrome (CRS). The clinical presentation of CRS ranges from simple fever to severe choc and is graded according to the SFGMTC criteria and depends on the presence of a fever ≥ 38°C and the severity of hypotension and/ or hypoxia, (Table 2)[46,47]. In the MajesTEC-1, MagnetisMM-3 and MonumenTAL-1 studies, the rates of CRS were similar with 72%, 56% and 75% of patients respectively including very few grade ≥3 events (<1%)[40–42.]

Neurotoxicity, including immune effector cell-associated neurotoxicity syndrome (ICANS), is thought to result from the disruption and the activation of by-standing immune cells in the central nervous system. Neurotoxicity associated with BsAb treatment is rare and typically develops concurrently with, or shortly after, CRS. Symptoms often begin with word-

finding difficulties, confusion, aphasia, and impairment of fine motor and cognitive skills, and might induce somnolence, seizures, and cerebral oedema[48–50]. Severity of ICANS is graded according to the ICE score *(Appendix 1)*, the level of consciousness and neurological symptoms, (*Table 2)*[51]. ICANS in the MajesTEC-1, MagnetisMM-3 and MonumenTAL-1 trials were reported in 3% of patients for Teclistamab and Elranatamab and 10% with Talquetamab without any events of grade >3.

Grade	CRS	ICANS
1	Fever ≥ 38°C; without hypotention or hypoxia	ICE :7–9 ; Awakens spontaneously
2	Fever ≥ 38°C; and hypotension responding to fluids or low dose vasopressors; and/or hypoxia requiring ≤ 40% Fi02	ICE :3–6 ; Awakens to voice
3	Fever ≥ 38°C; and hypotension requiring high dose vasopressor; and/or hypoxia requiring ≥ 40% Fi02	ICE : 0–2 ; Awakens only to tactile stimulus Any clinical seizure focal or generalized resolving rapidly or nonconvulsive seizures on EEG resolving with intervention Focal/local oedema on neuroimaging
4	Fever ≥ 38°C; and life-threatening hypotension and/or hypoxia requiring mechanic ventilation	ICE : 0 ; Stupor or coma Prolonged seizure (>5 min) or repetitive clinical or electrical seizures without return to baseline in between Deep focal motor weakness Diffuse cerebral oedema on neuroimaging; Decerebrate or decorticate posturing

Table 2. Grading of CRS and ICANS, adapted from CTCAE v5, SFGMTC criteria and EBMT/EHA CAR-T Cell Handbook, Jeremy H. Rees[51].

Progressive step-up of doses of BsAb and premedication with dexamethasone prevents the occurrence and severity of CRS and ICANS. Management of CRS and ICANS includes analgesics and antipyretics, and the addition of antibiotics if infection cannot be ruled out. If there is no improvement after 72 hours, treatment with tocilizumab (anti-IL6-receptor), although not efficient in ICANS, or corticosteroids and anakinra (anti-IL1-receptor) may be introduced. ICANS also requires the realization of additional tests such as EEG (electroencephalogram) or MRI to exclude other causes and antiepileptic treatment is often added[49], (*Table 3).*

Grade	Management of CRS	Management of ICANS
1	Observation • If persistent grade 1 (>24–48 h), early use of tocilizumab is encouraged	Observation • Can consider early dexamethasone in high-risk patients • Consider non-sedating anti-epileptic drugs
2	Tocilizumab 8 mg/kg • If no improvement, consider adding second line treatment (steroids)	Dexamethasone 10 mg every 12 h • If no improvement after 48 h, consider high dose dexamethasone (20 mg every 6 h) and alternative agents such as anakinra • Start non-sedating anti-epileptic drugs • Consider EEG and CT/MRI imaging
3	Tocilizumab plus dexamethasone 10 mg every 6 h • Transfer the patient to ICU • Consider high-dose steroids and salvage CRS treatment (anakinra)	Dexamethasone 10 mg every 6 h • If no improvement after 24 h consider high dose dexamethasone (20 mg every 6 h), high dose methylprednisolone (1–2 g per day) and/or alternative agents such as anakinra • Start non-sedating anti-epileptic drugs if not on already • Perform CT/MRI imaging, consider EEG • Consider CSF evaluation for other causes and pressure measurement • Transfer the patient to ICU
4	Tocilizumab plus high-dose steroids • Transfer the patient to ICU • Consider high-dose steroids and salvage CRS treatment (anakinra)	Dexamethasone 10 mg every 6 h • In dexamethasone refractory patients, consider high dose methylprednisolone 2 mg/kg every 12 h • For refractory patients consider alternative therapies (IL-1 blockers, such as anakinra) • Start non-sedating anti-epileptic drugs if not on these already • Perform CT/MRI imaging, consider EEG (if not previously done) • Consider CSF evaluation for other causes and pressure measurement (if not previously done) • Patient should be in the ICU

Table 3. Recommendations for management of CRS and ICANS grade of severity according to IMWG[49], ICU=intensive care unit, MRI = magnetic resonance imaging, EEG= electroencephalograms, CSF = Cerebral spinal fluid.

b) GPRC5D specific toxicities

The specific localisation of GPRC5D on keratinocytes is responsible for adverse events associated with Talquetamab treatment such as dysgeusia, dysphagia and rash. In the MONUMENTAL-1 study, 60% of patients experienced dysgeusia, 56% dysphagia and 28% weight loss. Theses “on target off tumor” toxicities are reversible over time but can nevertheless have an important impact on patients’ quality of life. The use of topical corticosteroids, artificial saliva sprays, emollient creams or bicarbonate mouthwashes can help manage these symptoms[42,52,53].

c) Cytopenia and hypogammaglobulinemia

Cytopenias are commonly reported across BsAbs' clinical trials, including neutropenia (grade ≥3 22,1–64,2%), anemia (grade ≥3 22,4–37%), thrombocytopenia (grade ≥3 8,8–25,9%), and lymphopenia (grade ≥3 16,1–32,7%). Although these studies were conducted among a heavily pre-treated population likely with pre-existing poor bone marrow reserve, the depth of cytopenias increased during BsAb administration, suggesting a treatment related effect[40,41,54]. The underlying physiopathology of BsAbs mediated cytopenia is poorly understood and is probably the result of interrelated factors. Several studies have investigated the occurrence of cytopenias following CAR-T cells, highlighting an association between severe CRS and ICANS syndrome and cytopenias[55,56]. The peak level of inflammatory cytokines may contribute to bone marrow suppression and could also be involved in the hematological toxicities of BsAbs.

Management of cytopenias includes the use of granulocyte colony-stimulating factor (G-CSF) in patients with grade ≥3 neutropenia but it should not be initiated before the risk of CRS has subsided. Transfusional support is to be administered in cases of severe anemia or thrombopenia. Few information are available concerning the benefit of thrombopoietic or erythropoietic agents in patients treated with BsAbs but they may be considered in well controlled disease period[49].

Hypogammaglobulinemia (HGG) is frequent among patients with RRMM resulting from their underlying disease and previous lines of therapy and is further worsened by BsAb treatment. HGG rates in patients treated with BsAbs vary between 70% and 90% depending on the study and target. BCMA-targeted BsAbs are associated with an even higher rate of HGG. Lancman et al report 100% of patients with IgG<400mg/dl among Teclistamab responders[57]. The median time to onset of HGG was short (2.9 months in this study). Guidelines on intravenous immunoglobulin (IvIg) replacement were issued by the Intergroupe Francophone du Myélome (IFM) in december 2022 and later by the International Myeloma Working Group (IMWG) in 2024[49.]

Cytopenias and HGG are well established risk factors for infections and concerns about high rates of infections have risen with the widespread use of BsAbs.

C. BsAbs and infections

As the development of BsAbs for multiple myeloma progressed, reports of serious infections emerged. In the phase I study of AMG 420, a BCMA-targeting BsAb, published in 2020, 70% of grade ≥3 adverse events were infectious[58]. In the MonumenTAL study, the rate of infections varied between 34% and 47% of patients depending on Talquetamab concentration with 7% of grade ≥3[54]. Infectious risk was striking in the MajesTEC-1 and MagnetisMM-3; with 80% and 70% of patients experiencing at least one infectious event and 55% and 40% of these events being grade ≥3, respectively[40,41]. Few retrospective real-word studies have been conducted to describe these events. Apart from one study based on 273 491 safety reports from a pharmacovigilance database[59], evidence on BsAbs related infectious events relied on monocentric and of limited scale studies, sometimes evaluating BsAbs directed against different antigens in the same population[57,60–64].

The main results regarding the incidence of infectious events in these studies are very heterogeneous, (*Figure 3).* The duration of treatment and follow-up varied across studies, which could explain the observed differences in incidence. In addition, details concerning the statistical model used were not always provided. Infections were mostly bacterial and viral, with no clear predominance of one type over the other across studies, (*Table S1).*

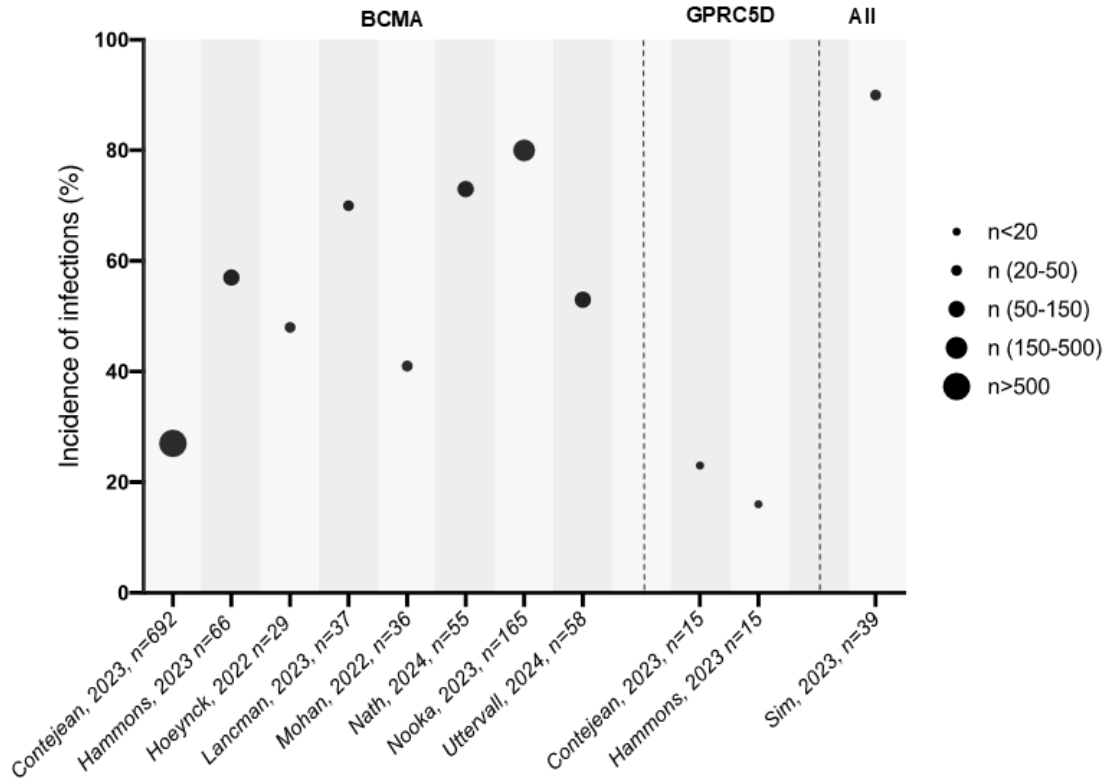

Figure 3. Incidence of infections across studies according to the number of patients included.

Two authors conducted a systematic review of studies reporting infectious complications in RRMM patients treated with all types of BsAbs. Mazahreh et al pooled data from 11 trials including 1185 patients and Reynolds et al 16 trials involving 1666 patients[65,66]. With a median follow up of 6,1 and 7,6 months respectively, the overall incidence of infections (and grade ≥3) in these two publications were 50% (24,5%) and 56% (24%). The risk of grade ≥3 infectious event was higher in patients treated with BCMA targeted BsAbs compared to non-BCMA BsAbs in both reports[65,66]

Data describing infectious complications in RRMM patients treated with BsAbs are therefore heterogeneous and based on small scaled studies. Furthermore, few real-world studies address the comparison of incidence between BCMA- and GPRC5D-targeting BsAbs and the possible risk factors for these infections.

Thus, we performed a multicentric 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.

II. Methods

A. Type of study and data sources

We performed a multicentre retrospective study in France through the Groupe Infection et Immunodepression network (G2i) of the Société de pathologie infectieuse de langue française and the IFM. Patients were identified in each participating center. Clinical and biological data were extracted from electronic health records and collected on a standardized case report form.

B. 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[67,68]. The MDI was defined as a 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. We only considered infections graded according to CTCAE (Common terminology criteria for adverse events) v5.0 affecting the patient's management 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 BsAb's administration, 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 lifethreatening infections; and grade 5 infections which contributed to death[68]. CRS, and ICANS were defined according to published criteria[47]. HGG was assessed by subtracting out the monoclonal Ig and defined as Ig < 400 mg/dL. Patients with MM refractory to IMiDs, PIs, and antiCD38 monoclonal Abs, were referred to as triple-class refractory.

C. 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 (nIRB00011642) 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.

D. Statistical analysis

The primary objective was to describe the occurrence of all infections affecting patient management and detail the infection's 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 Kruskall-

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 c2 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[69].

E. 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).

III. Results

A. Patients' characteristics

We identified 229 patients treated with BsAb in 14 centres with a median follow-up of 7 months (IQR: 4-12) (*Figure 4A*). Two hundred patients (87%) received BCMA-targeting BsAb (Teclistamab [n = 153] or Elranatamab [n = 47]) and 29 (13%) received GPRC5D targeting BsAb (Talquetamab). The main baseline characteristics of the patients are presented in *Table 4*. At the end of follow-up, 74 patients (32%) had died.

B. 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, (*Figure 4B 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 5)*. Among the MDI, 92 (56%) were

bacterial, 63 (38%) were viral and 8 (5%) were fungal *(Figure 4C and D).* Two (1.2%) infectious events were from a parasite. Most bacterial infections (n=65/165, 39%) were associated with the gastrointestinal tract (*Enterobacteriaceae,* enterococci, anaerobic bacteria). The most common viral infection was SARS-CoV-2 (n=21/165, 13%) followed by influenza/parainfluenza viruses (n=14/165, 8%) and cytomegalovirus (n=8/165, 5%). Invasive fungal diseases were due to *Aspergillus spp.* (n=6)*, Scedosporium spp.* (n=1) and *Pneumocystis jirovecii* (PJP) (n=1). There were also two cases of JC virus, one case of disseminated toxoplasmosis and one giardiasis.

One hundred and thirty-three (61%) infections occurred in patients with HGG <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 S2*. 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, (*Figure 4D, E, F*). All grade 4-5 or requiring ICU admission infections involved patients undergoing BCMA-targeting BsAb. Among the 234 infectious events, 103 (44%) influenced 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 S3 and S4)*, respectively.

Variables	Total (n=229)	BCMA-targeting BsAbs[a] (n=200)	GPRC5D-targeting BsAb[b] (n=29)
Age (years), median [range]	67 [38-85]	67 [38-85]	66 [49-83]
Women, *n* (%)	112 (49)	92 (46)	20 (69)
Immunochemical 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, *n*=225 [range]	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 neutropenia < $0.5x10^9$/L during BsAb treatment	19/114 (17)	18/109 (17)	1/5 (20)

Table 4. Characteristics of the 229 MM patients on BsAb therapy.
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.
Changes in denominators in the table indicate missing data.

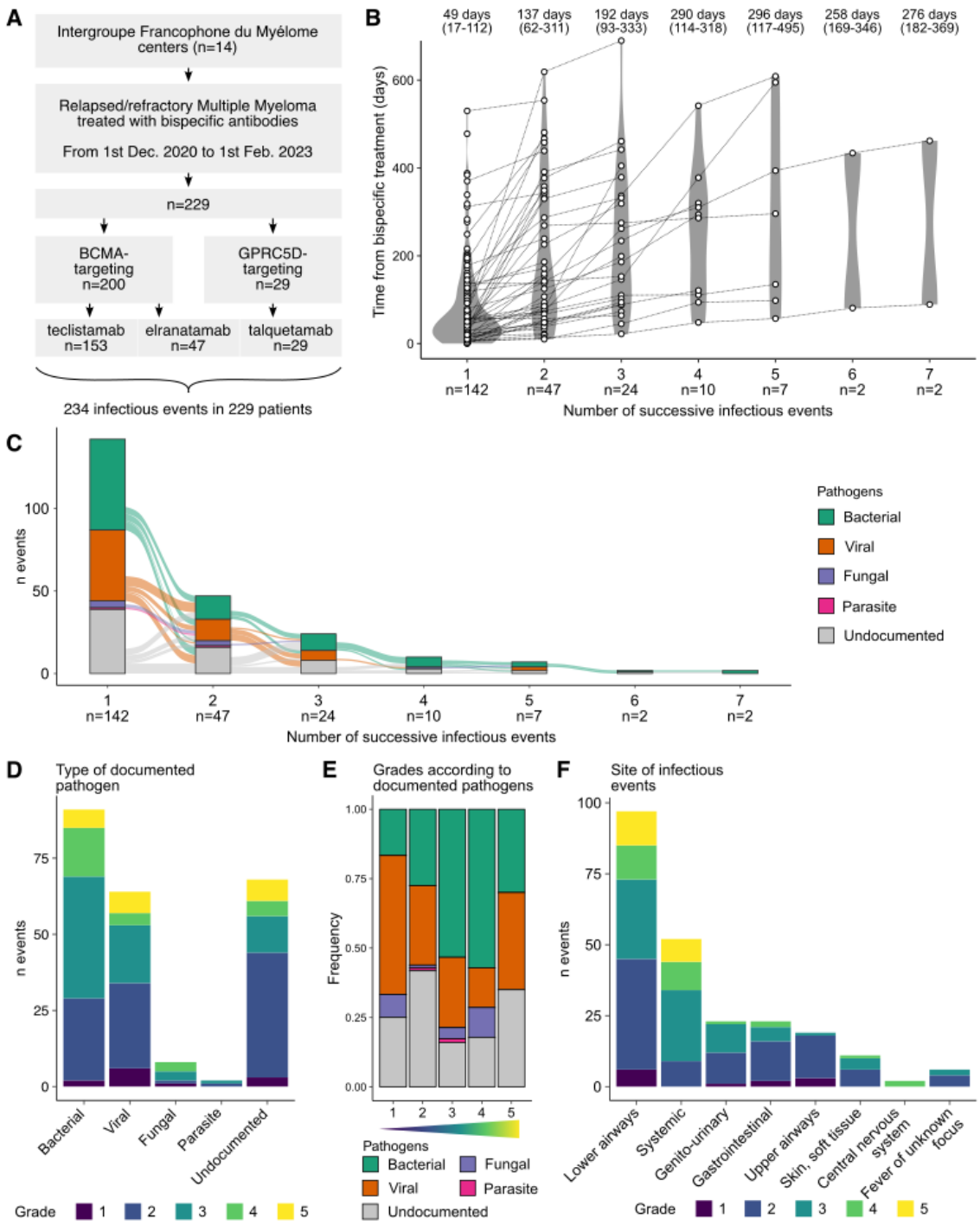

Figure 4. Main characteristics of infections. (A) Flow diagram showing the study design and main groups of included patients. **(B)** Violin plots and dot plots depicting the time from bispecific antibody treatment to infections according to the number of successive infections. Each dot represents an 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 events according to the pathogen documentation **(D)** Stacked bar plot reporting the number of infections according to the type of pathogen. Plots are colored 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 bacteremia, viremia, fungemia and infections affecting multiple organs. Plots are colored according to the grade of the recorded even

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 *, *n*(%)	**n=165**
Bacterial	**92/165 (56)**
Enterobacteriaceae	48/165 (29)
Pseudomonas aeruginosa and other non-fermentative gram-negative bacteria	13/165 (7)
Anaerobic bacteria	11/165 (6)
Enterococci	6/165 (4)
Staphylococci	5/165 (3)
Streptococci [a]	4/165 (2)
Haemophilus influenzae	4/165 (2)
Neisseria	1/165 (1)
Viral	**63/165 (38)**
Respiratory viruses [b]	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)**
Aspergillus spp.	6/165 (4)
Scedosporium spp.	1/165 (1)
Pneumocystis jirovecii	1/165 (1)**)**
Parasites	**2/165 (1)**
Toxoplasmosis	1/165 (1)
Giardiasis	1/165 (1)
Undocumented	**69 (29)**
Grade of infection [$], *n*(%)	
1	12/234(5)
2	98/234 (41)
3	75/234 (32)
4	28/234 (12)
5	20/234 (9)

Table 5. Characteristics and grades of infections impacting patient management

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

[*] from 159 MDI of which 6 were co-infections.

[a] including *S. pneumonia* ; [b] including SARS-CoV-2 (n=21), influenza/parainfluenza viruses (n=14), rhinovirus (n=2), respiratory syncytial virus (n=2) and metapneumovirus (n=1).
[$] n=1 missing data

C. 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 GPR5CD-targeting BsAb, (*Figure 5A 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), 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), (*Figure 5C)*. 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 first 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 (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 of infections. 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).

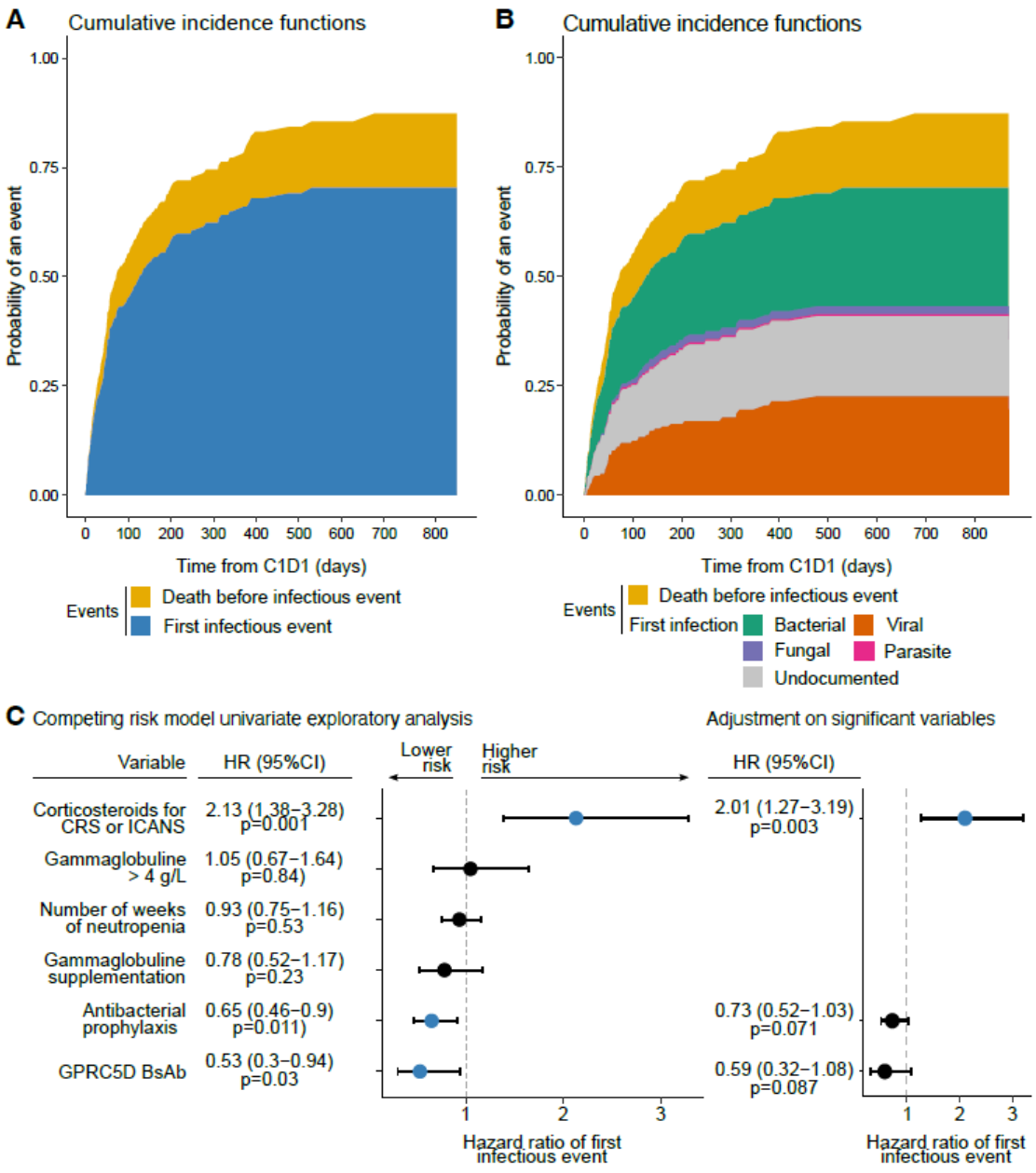

Figure 5. Cumulative incidence of all grades first infection. (A) Cumulative incidence function (CIF) of first infection. Death before first infection was used as a competing risk event. (B) The CIF of the first infection according to pathogen. Death was also used as a competing risk event. (C) Forest 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.

IV. Discussion

In this large-scale real-world multicentric study, we found a global cumulative incidence of first infections impacting patient management of 70%. Grade ≥ 3 infections accounted for more than half of all the events (53%). Predominant documentation was bacterial (n=92, 56%) and the most common site of infection was the respiratory tract (n=116, 50%). GPRC5D-targeting BsAbs were associated with a lower risk of first infection in the univariate analysis. In the multivariate model, only the use of corticosteroids for CRS/ICANS was associated with a higher risk of first infection.

The risk of acquiring infections in MM patients treated with BsAbs is multifactorial[70]. First, the abnormal expansion of clonal plasma cells in the bone marrow disrupts immune homeostasis, leading to B-cell depletion and cytopenia including neutropenia. Tumoral plasma cells produce only one type of immunoglobulin, combined with the reduced B-cell repertoire, result in immunoparesia and HGG hampering humoral immune response[71,72]. MM is also associated with a downregulation of the immune system and induces T-cell dysfunction[72].

Second, previous therapies, particularly chemotherapy and high-dose melphalan with ACST, which was administered in 65% of patients in our study, alter the immune system and enhance repeated antigen stimulation and T-cell exhaustion[73].

Finally, BsAbs treatment has also been shown to upregulate markers of T-cell exhaustion, leading to reduced T-cell functionality and impaired response to infections[16]. BsAb-targeting therapy is additionally associated with significant neutropenia, lymphopenia and HGG directly increasing the risk of acquiring infections, but also with the development of CRS, which is treated with immunosuppressive agents.[49]

Incidence of infections across trial is heterogenous, ranging from 13% with GPRC5D targeting BsAb in the Hammons *et al* study to 90% of patients treated with all types of BsAbs in the Sim *et al* study[57,60–63,74,75]. In our study, including a majority of patients treated with BCMA-targeting BsAbs, 142 patients (62%) presented an infectious event, which is consistent with the high infection rates observed in the MajesTEC-1 and MagnetisMM3 clinical trials[40,41].

We report a first infection cumulative incidence of 70% in the overall population. 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 may have overestimated the risk[76]. 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. The median follow-up duration in this study was relatively short at 7 months. However, as the median time to first infection was only 49 days, this is likely to have minimal impact on the cumulative incidence estimate.

Using the Fine and Gray model, we performed univariate analysis to identify variables associated with infectious events and found that GPRC5D-targeting BsAb and antibacterial prophylaxis were associated with a lower risk and the use of corticosteroids with a higher risk. Only the use of corticosteroids for CRS/ICANS was significant in the multivariate analysis. To compare our results with previous studies, we performed a second analysis with a Cox model and obtained similar results although GPRC5D and bacterial prophylaxis were significant with this model *(Fig S2).*

The cumulative incidence of first infections was higher among patients treated with BCMA-targeting BsAbs (73%) compared to GPRC5D (51%). Similarly, Hammons *et al* reported higher rates of infectious events under BCMA-targeting BsAb compared to GPRC5D-targeting BsAb[60]. Contejean *et al* found a higher number of reported infections with BCMA-targeting BsAbs than with other BsAb[59]. Mazareh and Reynold, in their meta-analysis of clinical trials also report an increased risk of infection associated with BCMA-targeting BsAbs compared to non-BCMA BsAbs but only for infections grade ≥3 and not for all grades[65,66]. Although the lack of statistical power due to the small number of patients treated with GPRC5D-targeting BsAb may have contributed to the inconsistent results between the two multivariate analysis models we used, our data are in line with a higher incidence of infections with BCMA targeting BsAb.

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. This difference may be attributable to a center effect, as patients treated with Talquetamab were recruited from only two centers. Another possible explanation could be that physicians became more experienced in managing CRS over time, leading to the more frequent and early use of tocilizumab for low-grade CRS. Although the risk of infection 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[77]. 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 [50].

Preventive measures that aim to mitigate the risk of infection in patients with MM are of tremendous importance. Previous studies have shown that HGG is associated with an increased risk of infections and have underlined the protective effect of immunoglobulin supplementation[57]. Lancman *et al*, showed a 90% reduction in grade 3–5 infections in patients receiving intravenous immunoglobulin [57,78]. In our study, hypogammaglobulinaemia and immunoglobulin substitution were not significantly associated with the risk of infection. Guidelines concerning IvIg replacement were issued by the IFM group in december 2022, and therefore not all patients eligible for immunoglobulin replacement were supplemented. In addition, 50% of patients receiving immunoglobulin supplementation had persistent HGG at the time of infection, with serum levels remaining below 400 mg/dL. Nevertheless, the high frequency of bacterial respiratory infections supports immunoglobulin supplementation in BsAb-treated patients with severe HGG or repeated infections as recommended by the IMWG in 2024[49]. Considering the widespread prevalence of HGG <200mg/dl expected in BCMA treated patients, supplementation is often initiated within the first month.

Patients should receive yearly *influenza* vaccination, updated SARS-CoV-2 vaccination, pneumococcal vaccination, and recombinant varicella zoster vaccination[50,79] . The benefit of the recently available RSV (respiratory syncytial virus) vaccines will have to be considered [80].

Cases of opportunistic infections including *toxoplasmosis*, PML, PJP and viral reactivation have been reported in our study and also in previous work[57,59,60,63,74,75] *(Table S1)*, some of which were rarely observed in multiple myeloma patients treated with previous therapies, highlighting the profound immunosuppression induced by BsAbs[81–83]. Baseline assessment of serological status for EBV, CMV, HSV, and HIV must be performed prior to treatment initiation. 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[49,50,79]. Systematic monitoring is not recommended for these pathogens but must be considered in the event of fever or symptoms, especially CMV DNAemia since it was not exceptional in our study.

Antibacterial prophylaxis was also associated with a lower risk of infection in the univariate analysis for all types of infectious events and was confirmed in an analysis centered on bacterial infections *(Fig S3)*. Conversely, general antibacterial prophylaxis is not recommended except in cases of prolonged neutropenia or history of recurrent bacterial

infections[49,50,79]. Given the high frequency of bacterial infections in our study, antibacterial prophylaxis may be discussed in high-risk patients and possibly limited to the first few months of treatment. The optimal choice of antibacterial prophylaxis remains to be defined. Although the IMWG guidelines recommend quinolones, the selection pressure for resistant organisms is a significant concern. Several centers prescribe amoxicillin or oracillin, which may be ineffective against certain bacteria, particularly some *Enterobacteriaceae*, identified as the most frequent bacterial pathogens in our and other studies.

Guidelines also recommend fluconazole prophylaxis in case of a history of fungal infection, prolonged neutropenia or steroid administration [49,50,79].Given that prolonged neutropenia was rare, dexamethasone therapy was rarely continued after step-up doses, and fungal infections were mainly caused by molds, we would instead advocate for the use of a prophylaxis active against molds in case of an important risk of fungal infection.

Finally, T-cell exhaustion induced by BsAbs can be reduced by treatment-free intervals and recent data on BCMA bispecific antibodies reported a decrease in the incidence of severe infections when switching from a once weekly to a once every 2 weeks or monthly dosing schedule[16,84,85]. These findings suggest that less intensive dosing over time or fixed-duration dosing might mitigate the infectious risk.

However, this study is limited by its retrospective nature and the heterogeneity of infections, prophylactic treatments 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 RRMM patients not receiving BsAb revealed an infection rate of 28.6%, including 6.5% of grade 3 to 4 events[14].

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, this study is to our knowledge, the first large-scale real-world multicenter series of BsAb-treated patients reported to date and provides insights into the epidemiology and

characteristics of infections associated with MM BsAb treatment. 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.

V. References

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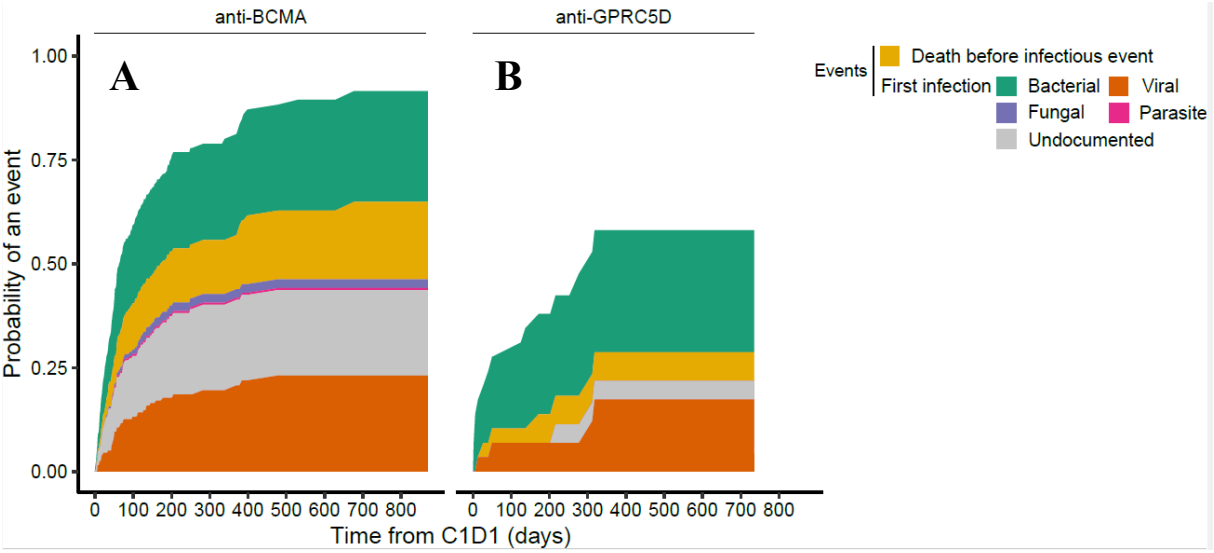
VI. Supplementary data

Study	Incidence of infections, % (grade≥3, %)			Median time to infection (days)	Documentation, %				Risk factors
	All	BCMA	GPRC5D		Bacterial	Viral	Fungal	Opportunistic	
Contejean et al, AMJ, 2023		n=692; 27,4% (88%)	n=17; 23%	44				5% 5PJP	
Hammons et al,Haematologica, 2023		n=66 57% (58%)	n=15 13% (36%)		52%	40%	7%	3PJP 2 asp	-BMCA therapy, -history of infections, -baseline lymphopenia, -baseline HGG
Hoeynck et al, Blood,2022		n=29 56% (30%)							
Lancman et al, Blood 2023		n=37 70%, (30%)		102	43%	46%	11%	6 PJP 1 PML	-HGG (infection grade ≥3)
Mohan et al, Blood advances, 2023		n=36 41%		49					
Nooka et al, 2023, Cancer		n=132 80% (55%)		51				9,1% 7PJP, 1 asp, PML	
Nath et al, Blood Cancer Journal, 2024		n=55 78% (40%)			53%	42%	3%	1 PJP	
Sim et al, Blood Cancer journal, 2023	n=39 90% (20%)				39%	58%			
Utervall et al, Cancer Medecine, 2024		n=58 53%						2 PJP 1 PML	

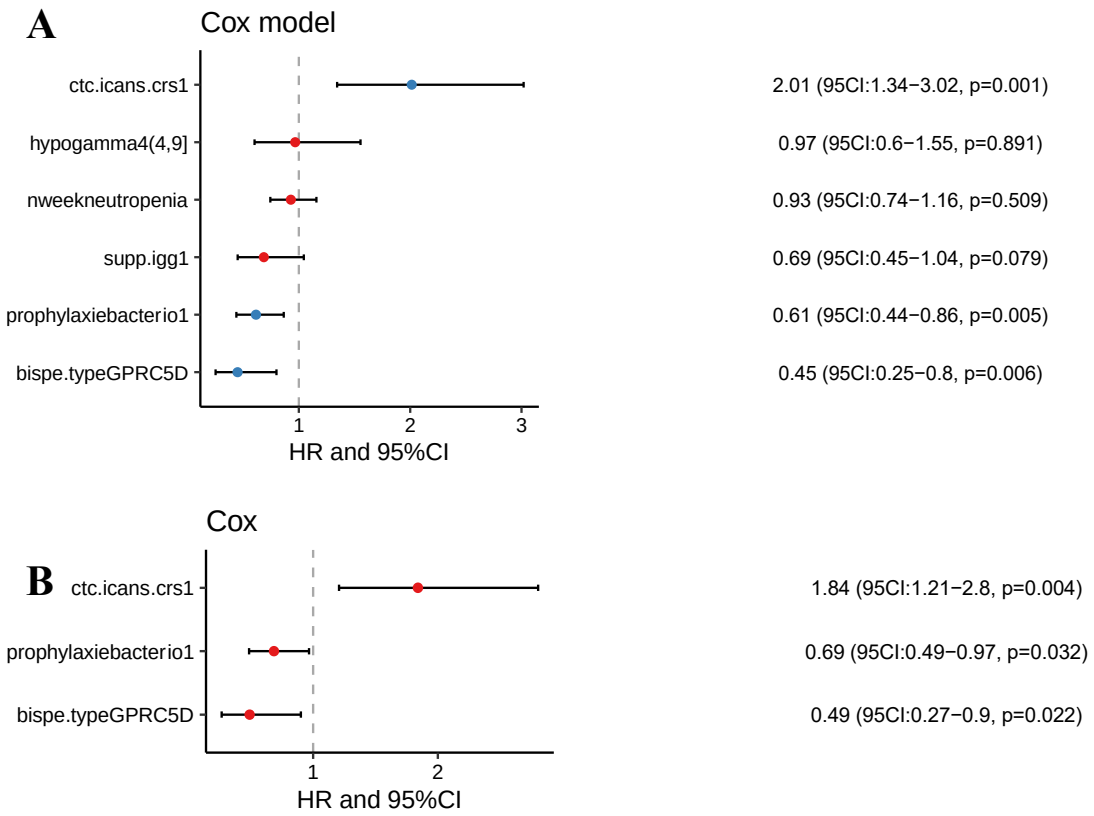
Supplementary Table 1. Description of characteristic and incidence of infections occurring in patients treated with BsAbs across trial
PJP = Pneumocystis jirovecii, asp = Aspergillus spp, PML = Progressive multifocal leukoencephalopathy (JC virus).

Prophylaxis (number of documented cases), % (*n*)	Total (n=234)	BCMA-targeting BsAbs (n=216)	GPRC5D-targeting BsAb (n=18)
Bacterial prophylaxis[a] (*n*=223)	47 (104)	44 (91)	76 (13)
Viral prophylaxis[b] (*n*=226)	91 (206)	90 (188)	100 (18)
Trimethoprim-sulfamethoxazole or atovaquone prophylaxis (*n*=226)	73 (166)	72 (160)	89 (16)
Pentamidine prohylaxis (*n*=224)	11 (25)	12 (25)	0 (0)

Supplementary Table 2. Prophylaxis at time of first infectious event.
[a] Oracilline, Levofloxacine or Amoxicillin
[b] Aciclovir or Valaciclovir
[c] Posaconazole, Fluconazole or Isavuconazole



Supplementary figure 1. Cumulative incidence of first infection according to BsAb class. (A) Cumulative incidence function (CIF) of first infection in patients treated with BCMA-targeting BsAb. Death before first infection was used as a competing risk event. (B) CIF of first infection in patients treated with GPRC5D-targeting BsAb. Death was also used as a competing risk event.



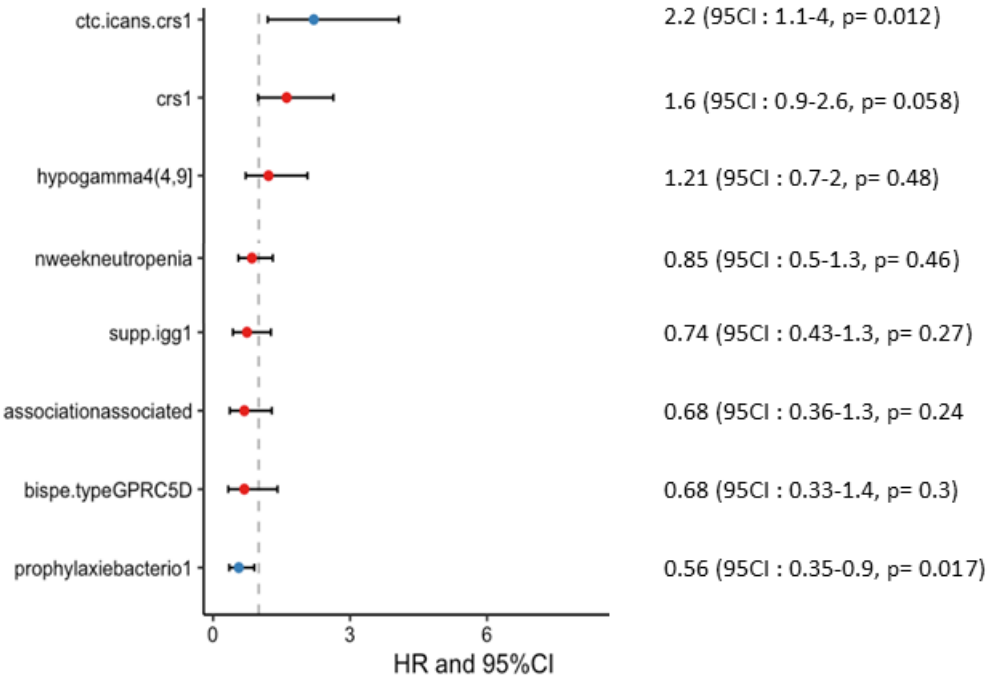
Supplementary figure 2. Forest plot summarizing univariate **(A)** and multivariate **(B)** analysis of variables associated with first infection. A Cox model was used to compute hazard ratio (HR), 95% confidence intervals (95%CI) and p-values.

Variables	Total (n=30)
Site of infection, n(%)	
Systemic	8 (26)
Respiratory tract	16 (53)
Gastrointestinal tract	2 (6)
Genitourinary tract	3 (10)
Skin and soft tissue	1 (3)
Pathogens isolated, n(%)	
Bacterial	11 (36)
Enterobacteriaceae	10 (33)
Enterococci	1 (3)
Viral	6 (20)
Covid 19	3 (10)
Influenza virus	2 (6)
VRS	1 (3)
Parasites	1 (3)
Toxoplasma gondii	
Fungi	1 (3)
Scedosporium spp.	
Undocumented	11 (36)
Grade of infection, n(%)	
1	1(3)
2	12 (40)
3	7 (23)
4	4 (13)
5	6 (20)

Supplementary table 3. Characteristics of first infections in patients treated with corticosteroids for CRS/ICANS.

Variables	**Total (n=30)**
Site of infection, *n* (%)	
Systemic	10 (33)
Respiratory tract	17 (57)
Gastrointestinal tract	1 (3.3)
Genitourinary tract	1 (3.3)
CNS	1 (3.3)
Pathogens isolated *, *n* (%)	***n*=24**
Bacterial	**13 (43)**
Enterobacteriaceae	9 (30)
Pseudomonas aeruginosa and other non-fermentative Gram-negative bacteria	3 (10)
Streptococci [a]	1 (3.3)
Viral	**9 (30)**
Covid 19	6 (20)
Influenzae	2 (6.6)
Enterovirus	1 (3.3)
Fungi	**2 (6.6)**
Aspergillus spp.	1 (3.3)
Pneumocystis jirovecii	1 (3.3)
Undocumented	**6 (20)**
Grade of infection [$], *n* (%)	
3	1 (3)
4	17 (57)
5	12 (40)

Supplementary table 4. Characteristics of first infections in patients admitted in ICU.

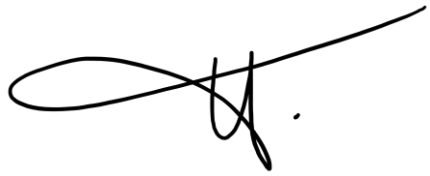


Supplementary figure 3. Forest plot summarizing univariate analysis of variables associated with first bacterial infection with death defined as a competing risk. Fine and Gray models were used to compute hazard ratios (HR), 95% CI and p-values.

Immune Effector Cell Encephalopathy (ICE) Score
• *Orientation:* Orientation to year, month, city, hospital: 4 points • *Naming:* Ability to name 3 objects (e.g., point to clock, pen, button): 3 points • *Following commands:* Ability to follow simple commands (e.g., "show me 2 fingers" or "close your eyes and stick out your tongue"): 1 point • *Writing:* Ability to write a standard sentence (e.g., "our national bird is the bald eagle"): 1 point • *Attention:* Ability to count backwards from 100 by 10: 1 point

Appendix 1. ICE score

Vu, le Directeur de Thèse



Vu, à Tours
le 5/11/2024

Vu, le Doyen
De la Faculté de Médecine de Tours
Tours, le

académie d'Orléans-Tours | université de TOURS | Faculté de médecine

CELLERIN Elise

59 pages – 9 tableaux – 8 figures

Résumé :

Introduction : Les anticorps bispécifiques (AcBs) sont des nouvelles immunothérapies efficaces chez les patients avec un myélome multiple en rechute ou réfractaire (MMRR). Cependant, les complications infectieuses sont fréquentes principalement chez les patients traités avec des AcBs ciblant le BCMA. Cette étude a pour objectif de décrire les caractéristiques des infections impactant la prise en charge des patients et de décrire l'incidence cumulative de la première infection ainsi que les variables associées à ce risque.

Méthode : Nous avons mené une étude rétrospective sur 14 centres français de l'Intergroupe Francophone du Myélome incluant tous les patients avec traités par AcBs anti-BCMA ou anti-GPRC5D entre décembre 2020 et février 2023 et avons rapporté tous les événements infectieux impactant la prise en charge du patient.

Résultats : Parmi les 229 patients inclus, 200 (87 %) étaient traités par un AcBs anti-BCMA, dont 153 par Teclistamab et 47 avec l'Elranatamab et 29 patients (13 %) par l'AcBs anti-GPRC5D, le Talquetamab. Les taux de CRS et ICANS tout grade étaient similaires dans les 2 groupes (60 à 66% et 5 à 7% respectivement). Aucun des patients du groupe traité par anti-GPRC5D n'a reçu de corticoïdes pour la gestion d'un CRS/ ICANS (contre 19 % chez les patients traités par anti-BCMA) mais l'utilisation du Tocilizumab était plus fréquente (41 % contre 23 %). Durant la période de l'étude, nous rapportons 234 événements infectieux. Cent quarante-deux patients (62%) ont présenté au moins un évènement infectieux avec une durée médiane avant la première infection de 49 jours. Les infections de grade ≥ 3 représentaient 53% des infections. Une majorité des infections étaient d'origine respiratoire (50%) ou disséminée (22%) et principalement d'origine bactérienne (56%) L'incidence cumulative de première infection dans la population totale était de 70%. Dans l'analyse univariée, l'utilisation des corticostéroïdes pour la gestion CRS/ICANS était associée à une augmentation du risque de la première infection tandis que les AcBs ciblant le GPRC5D et l'antibioprophylaxie étaient associés à une réduction du risque de première infection. Le modèle multivarié de Fine et Gray a montré que seule l'utilisation de corticostéroïdes pour la gestion d'un CRS ou ICANS était associée à une augmentation du risque de la première infection (HR = 2.01; 95% CI, 1.27-3.19).

Conclusion : Cette étude souligne la forte proportion d'infections sévères chez les patients traités par AcBs. Ces données renforcent l'importance des prophylaxies anti-infectieuses et encouragent une utilisation précautionneuse des corticoïdes dans cette population

Mots clés : Myélome multiple, Immunothérapie, Anticorps bispécifiques, Infections, Facteurs de risques

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