Annals of Hematology
https://doi.org/10.1007/s00277-025-06645-y

RESEARCH

Infection events in patients with newly diagnosed multiple myeloma with anti-CD38 monoclonal antibody-based first line regimens: A multicentric Italian experience

Angela Rago[1,11] · Francesca Fioritoni[2] · Carmine Liberatore[2] · Stefano Pulini[2] · Francesca Fazio[3] · Maria Teresa Petrucci[3] · Valerio De Stefano[4] · Elena Rossi[4] · Tommaso Za[4] · Francesca Di Landro[4] · Laura De Padua[5] · Masssimo Offidani[6] · Sonia More[1] · Annibali Ombretta[7] · Valeria Tomarchio[7] · Maria Antonietta Tafuri[7] · Alfonso Piciocchi[8] · Luca Franceschini[9] · Alessia Fiorini[10] · Tommaso Caravita di Toritto[1]

Received: 29 May 2025 / Accepted: 18 September 2025

Abstract

Multiple myeloma (MM) is a malignancy characterized by the clonal proliferation of plasma cells. It accounts for approximately 1% of all cancers and is the second most common hematologic malignancy after lymphoma. Infections represent a major cause of morbidity and mortality in patients with newly diagnosed multiple myeloma (NDMM), contributing to approximately 45% of early deaths, particularly in elderly individuals and during the initial months of therapy. Current treatment options for MM, including anti-CD38 monoclonal antibodies (CD38 mAbs), proteasome inhibitors, immunomodulatory drugs (such as lenalidomide and thalidomide), and glucocorticoids, have significantly improved clinical outcomes in NDMM patients. However, these therapies are associated with an increased risk of infections. Daratumumab (Dara), an anti-CD38 monoclonal antibody, is a key component of modern MM treatment and is approved for both NDMM and relapsed/refractory MM (RRMM). While Dara has improved patient outcomes, it has also altered the frequency and epidemiology of infections in this population. We conducted a retrospective analysis of 472 NDMM patients treated with Dara-containing regimens at 10 centers of the European Myeloma Network Italy (EMN-I) between 2020 and 2023 to assess the incidence of infectious events (IEs). Among these patients, 148 (31.3%) experienced infectious complications during therapy. No significant differences in infection rates were observed across the three treatment subgroups analyzed. In our experience, the addition of Dara during the induction phase did not increase the frequency, severity, or duration of infections in any of the three cohorts. Although the difference was not statistically significant, we observed an earlier onset of infections in the D-VTD group compared to the others. Further studies are needed to better define the incidence of infections in this patient population and to identify risk factors for infection. This may also inform the role of prophylactic strategies in the clinical management of NDMM.

Keywords Multiple myeloma · Infection disease · Monoclonal antibody

✉ Angela Rago
angela.rago@aslroma1.it

[1] UOSD Ematologia, ASL Roma 1, Roma, Italy

[2] Department of Medicine and Aging Sciences, "G D'Annunzio" University, Chieti-Pescara, Italy

[3] Azienda Ospedaliera Universitaria Policlinico Umberto I, Ematologia, Roma, Italy

[4] Department of Radiological and Hematological Sciences, Catholic University, Fondazione Policlinico Gemelli IRCCS, Roma, Italy

[5] Trapianto di cellule staminali e Terapia genica, Ospedale F. Spaziani, UOC Ematologia, Frosinone, Italy

[6] Clinica di Ematologia, Azienda Ospedaliero Universitaria delle Marche, Ancona, Italy

[7] Policlinico Universitario Campus Bio-Medico e, Dipartimento di Medicina e Chirurgia Università Campus Bio-Medico, Roma, Italy

[8] GIMEMA Data Center, Fondazione GIMEMA Franco Mandelli Onlus, Rome, Italy

[9] Dipartimento di Oncologia-Ematologia Fondazione Policlinico Tor Vergata, Roma, Italy

[10] UOC Ematologia, Ospedale Santa Rosa, Viterbo, Italy

[11] Haematology Unit, ASL ROMA 1, Santo Spirito Hospital of Rome, Lungotevere in Sassia 1, Rome 00198, Italy

Published online: 11 October 2025

Introduction

Multiple myeloma (MM) is a malignancy characterized by the abnormal proliferation of clonal plasma cells and accounts for approximately 1% of all neoplastic diseases, making it the second most common hematologic malignancy after lymphoma. The median age at diagnosis is 69 years [1, 2]. MM is associated with suppression of normal immunoglobulin synthesis, leading to impaired humoral immunity. Additionally, MM patients exhibit dysfunction in both cellular and innate immunity [3].

Infection is a major cause of morbidity and mortality in newly diagnosed multiple myeloma (NDMM) patients, accounting for approximately 45% of early deaths, particularly in the elderly and within the first months of treatment initiation [4]. Compared to the general population, MM patients have a sevenfold increased risk of developing infections during the course of their disease; this risk rises to tenfold when considering viral infections alone.

Despite significant advances in therapy, MM remains incurable and follows a pattern of repeated relapses after initial response. In recent decades, however, therapeutic developments have markedly improved survival rates and quality of life for MM patients [1].

Available treatments—including anti-CD38 monoclonal antibodies (CD38 mAbs), proteasome inhibitors (PIs), immunomodulatory agents (IMiDs such as lenalidomide), and corticosteroids—have significantly enhanced outcomes for NDMM patients but also increase susceptibility to infections [5, 6]. Corticosteroids, an essential part of MM therapy, are well known for their immunosuppressive properties. Proteasome inhibitors, while effective, can impair T-cell function and are associated with increased risk of varicella-zoster virus (VZV) reactivation [7, 8].

IMiDs may offer some protection through enhancement of NK and T-cell activity; however, they are associated with cytopenias and have been linked to higher infection rates in clinical practice [4, 9, 10]. Similarly, anti-CD38 mAbs reduce NK cell populations and regulatory T-cells, contributing to increased rates of VZV reactivation and hepatitis B virus (HBV) reactivation [10, 11].

Daratumumab (Dara), a CD38 mAb, is approved for use in both NDMM and relapsed/refractory MM (RRMM). Its introduction has significantly improved patient outcomes but has also altered the incidence and epidemiology of infections in this population [11–14]. To investigate this issue, we conducted a real-world, retrospective analysis involving a large cohort of NDMM patients treated across ten centers in Italy. The primary objective was to evaluate the number, type, and risk of infectious events (IEs) associated with the use of Dara in the induction phase, in both transplant-eligible and transplant-ineligible patients.

A major limitation of this study is its retrospective design, which introduces the possibility of selection bias. Moreover, we did not include a control group of MM patients who did not receive Dara, which limits the ability to directly assess the additional risk of infection attributable to Dara itself. Importantly, the primary aim of our study was to compare different Dara-based treatment combinations, rather than to comprehensively assess the overall infectious risk associated with Dara.

Patients and methods

Among the 472 NDMM patients treated with Dara-based combinations, we retrospectively analyzed the subset of 148 patients who developed at least one infectious complication during treatment. As some patients experienced multiple infectious episodes, the total number of infection events exceeds the number of individuals analyzed. All 472 patients received Dara-based regimens between 2020 and 2023. The aim was to evaluate the number, type, and risk of infectious events (IEs) in this population. Patients were divided into three treatment cohorts based on the induction regimen received: **Cohort A**: Daratumumab, bortezomib, melphalan, and dexamethasone (Dara-VMP); **Cohort B**: Daratumumab, lenalidomide, and dexamethasone (Dara-RD); **Cohort C**: Daratumumab, bortezomib, thalidomide, and dexamethasone (Dara-VTD). The study was approved by the local Ethics Committees of the participating centers. Diagnosis was established according to the International Myeloma Working Group (IMWG) consensus criteria, and prognostic risk and patient fitness were assessed using the International Staging System (ISS) and the frailty score, respectively [15, 16].

Antibiotic and antiviral prophylaxis were not administered according to a standardized protocol but were prescribed at the discretion of the treating physicians. Consequently, the initiation and type of prophylaxis varied across participating centers.

Baseline demographic characteristics, induction regimens, and infection-related data are summarized in Table 1.

Infectious events (IE) and prohylaxis.

Antibiotic and antiviral prophylaxis were not routinely administered during treatment. Pre-specified hematologic and biochemical parameters were collected, including absolute neutrophil and lymphocyte counts, as well as baseline immunoglobulin levels (IgA, IgM). Neutropenia was defined as an absolute neutrophil count $< 0.5 \times 10^9$/L, and lymphocytopenia as an absolute lymphocyte count $< 0.5 \times 10^9$/L.

Univariate analysis revealed significant associations between infectious events and several baseline parameters. Both pre-treatment neutropenia and lymphocytopenia

were strongly associated with an increased risk of infection ($p < 0.001$). Lower baseline serum levels of IgA and IgM were also significantly correlated with infectious complications ($p = 0.0066$ and $p = 0.0388$, respectively).

Each infectious episode was classified according to the International Immunocompromised Host Society (ICHS) criteria [17] as either: Microbiologically defined infection (MDI); Clinically defined infection (CDI) and Fever of unknown focus (FUF).

Infections were further graded for severity using the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 [10]. Pre-existing comorbidities were scored using the Charlson Comorbidity Index (CCI).

Among the 145 evaluable infectious episodes:29 (19.6%) were classified as MDI; 50 (33.8%) as CDI; 7 (4.7%) as FUF in 59 cases (39.9%), classification was not possible due to incomplete or insufficient clinical data.

Infections were also categorized according to the World Health Organization's International Statistical Classification of Diseases, 10th Revision (ICD-10) [18]. Based on this classification: Non-serious infections included upper respiratory tract infections, urinary tract infections, diarrheal illnesses, and skin infections. Serious infections were defined as those requiring hospitalization, including pneumonia, sepsis, complicated urinary tract infections, and other severe conditions.

Infection severity, graded by CTCAE v5.0, was as follows: Grade 1: 37%; Grade 2: 35%; Grade 3: 19%; Grade 4: 6%; Grade 5 (infection-related death): 3.6% Grading was not available in 64 cases due to incomplete documentation.

Statistical analysis

Baseline clinical and infection characteristics were summarized using median and range (min, max) for continuous variables and percentages for categorical variables. To determine clinical and treatment associated risk factors for infection, univariate analysis was performed with first episode of infection (MDI, CDI, FUF) and MDI as the main outcomes of interest. MDI was evaluated as it constitutes a proven infection. In univariate analysis non-parametric tests were performed for comparisons between groups (Chi-Squared and Fisher Exact test in case of categorical variables, Mann-Whitney and Kruskal-Wallis test in case of continuous variables). Survival curves (OS and PFS) were estimated according to the Kaplan-Meier product-limit method and were tested for significant differences using the log-rank test. All tests were 2-sided, accepting $p < 0.05$ as indicating a statistically significant difference and confidence intervals were calculated at 95% level. All analysis were performed using the R software.

Results

Cohort dara-VMP

Baseline characteristics of this cohort are summarized in Table 1. This subgroup included 20 patients who were ineligible for autologous stem cell transplantation. The median age was 74 years (range 69–76), with a male-to-female distribution of 12:8. Two patients (10%) were younger than 65 years, while the majority (18/20; 90%) were older than 65.

At diagnosis, the International Staging System (ISS) classification was as follows: stage I ($n = 3$), stage II ($n = 8$), stage III ($n = 3$), and unknown ($n = 6$). Based on frailty assessments, five patients were classified as fit, six as unfit, and two as frail; frailty status was unavailable for seven patients.

Baseline laboratory values included, the median haemoglobin (Hb) level was 11.15 g/dL (10.2–12), β2m 3.7 mg/dL (2.9–4.6), median monoclonal component (CM) was 3.96 g/dL 0.58–5.28), LDH were 187 (139–238). The white blood cell (WBC) was 6.000×10^9/L (range 4–11×10^9/L), absolute neutrophil count was 4.325×10^9/L (range 2.7–6.9×10^9/L), absolute lymphocyte count was 1.3×10^9/L (range 1-2.4×10^9/L). Plasma cell infiltration was 70% (range 60–90). Cytogenetic analysis at diagnosis was available in 19 of 20 patients (95%), and high-risk cytogenetics were identified in 7 of 19 patients (37%). The Immunoglobulin (Ig) dosage at diagnosis was: IgG 488 (range 331-1.019), IgA 114 (range 30-1705) and IgM 10 (range 7–24). Arterial hypertension ($n = 3$), cardiomyopathy ($n = 9$) and diabetes ($n = 1$) werethe most common comorbidities reported. Antiviral and antibacterial prophylaxis was given to 14/20 (70%) 13/20 (65%) patients, respectively. We considered all the prophylaxis interventions as given at any time points during the therapy.

The most common comorbidities were cardiomyopathy ($n = 9$), arterial hypertension ($n = 3$), and diabetes mellitus ($n = 1$). Antiviral prophylaxis was administered to 14 of 20 patients (70%), and antibacterial prophylaxis to 13 patients (65%). All prophylactic treatments were recorded regardless of timing during therapy.

Details on the number, type, and severity of infectious events (IEs) are shown in Table 2. A total of 20 IEs were reported: fever ($n = 4$), respiratory tract infection ($n = 1$), and unknown etiology ($n = 15$). Infection severity was graded as follows: grade 1 ($n = 2$), grade 2 ($n = 1$), grade 3 ($n = 1$), grade 4 ($n = 1$), and unknown in 15 cases.

The median time to IE onset was 48 days (range 7–161), and patients had received a median of 4 Dara-VMP cycles (range 3–8) at the time of infection. The median duration of infection was 6 days (range 5–6).

Table 1 Baseline characteristics stratified by treatment

VARIABLE	OVERALL 148 Pts	Cohort Dara-VMP 20 Pts	Cohort Dara-Vtd 48 Pts	Cohort Dara-Rd 80 Pts	*P*
Age, years (median, range)	71 (65–75)	74 (69–76)	74 (71–77)	62 (57–67)	*0.001*
Hb gr/dL (median, range)	11.6 (10.3–13.2)	11.1 (10.2–12)	11.5 (10.7-13.15)	11.6 (9.9–13.5)	*0.7*
Beta2M mg/L (median, range)	3.7 (2.5–4.7)	3.7 (2.9–4.6)	3.3 (2.1–5.3)	3.7 (2.5–4.7)	*0.7*
LDH U/L (median, range)	163 (131–201)	187 (139–238)	157 (132–209)	163 (131–189)	*0.4*
M-spike, gr/dL (median, range)	2.28 (0.58-5,28)	3.96 (0.58–5.28)	2.25 (1.06–3.58)	2.25 (1.0-4.9)	*0.6*
Gb median	16	6 (4–11)	3.8 (7-6.5)	2.4 (4–11)	*0.003*
N, median, range	2.8	4.3 (2.7–6.9)	4.1 (2-6.2)	3 (1.08–3.58)	*0.04*
L, Median, range	1.2	1.3 (1-2.4)	1.4 (0.6–2.2)	1.15 (1–2.0)	*0.8*
IgG, Median, range	74 (24–579)	488 (331-1.019)	56 (32–883)	53 (20–466)	*0.025*
IgA, Median, range	14 (1–41)	114 (30-1705)	15 (0–40)	15 (0–40)	*<0.001*
IgM, Median, range	1 (0–13)	10 (7–24)	1 (0–17)	1 (0–17)	*0.004*
ISS n, (%)	45(5)	3(21)	14(52)	28(47)	*0.1*
I	29(29)	8(57)	8(30)	13(22)	
II	25(25)	3(21)	5(19)	17(29)	
III	1(1)	0	0	1(1.7)	
NV	48	6	21	21	
UNK					
Fitness n, (%)	66(64)63.3)	5(38)	23(79)	38(62)	*0.01*
	30(29)	6(46)	5(17)	19(31)	
Fit	7(6.8)	2(15)	1(3.4)	4(6.6)	
Unfit	45	7	19	19	
Frail					
UNK					

Laboratory values at the time of infection were: IgG 440 (360–460), IgA 23 (8–30) and 9 (7–10). The WBC count at time of IE was 4.7×10^9/L (range 3.4–8.1) and absolute neutrophil count was 2.8×10^9/L (range 2.5–3.2).

Cohort dara-RD

We retrospectively reviewed data from 80 NDMM patients who developed infectious events (IEs) during treatment with the Daratumumab–Lenalidomide–Dexamethasone (Dara-RD) regimen. Baseline characteristics of this cohort are summarized in Table 1.

At diagnosis, the median age was 74 years (range 71–77). A total of 7 patients (8.8%) were under 65 years of age, while the majority (73/80; 91.2%) were over 65. The cohort included 46 males and 33 females. ISS stage at diagnosis was: stage I ($n=28$), stage II ($n=13$), stage III ($n=18$), and unknown in 21 patients.

Regarding fitness status, 38 patients were classified as fit, 19 as unfit, and 4 as frail; fitness status was unknown in 19 patients.

Cytogenetic data were available in 68 of 80 patients (85%), with 19 patients (28%) displaying high-risk abnormalities.

The most common pre-existing comorbidities were arterial hypertension ($n=28$), cardiomyopathy ($n=10$), and diabetes mellitus ($n=1$). Antiviral prophylaxis with acyclovir was administered in 58 patients (72%), and antibacterial prophylaxis in 57 patients (71%).

The median haemoglobin (Hb) level was 11.6 g/dL (9.9–13.5), β2m 3.7 mg/dL (2.5–4.7), median monoclonal component (CM) was 2.25 g/dL (1.06–3.58), LDH were 163 (131–189). The WBC was 2.410 (4–11) and neutrophil count median was 3×10^9/L (1.080–51450). The Ig dosage at diagnosis was: IgG 53 (range 20–466), IgA 15 (range 0–40) and IgM 1 (range 0–17). The cytogenetic analysis at diagnosis was present in 68/80 (85%) patients and of 19/80 (28%) had a high risk cytogenetic. At diagnosis, the most common comorbidities were: arterial hypertension ($n=28$), cardiomyopathy ($n=10$) and diabetes ($n=1$). Over time, antiviral prophylaxis with acyclovir was done in 58/80 (72%) and antibacterial prophylaxis in 57/80 (98%) patients.

Data regarding the number, severity, and type of infectious events are reported in Table 2. The 80 patients experienced various types of IEs, including: covid infection ($n=16$), cmv reactivation ($n=3$), pneumoniae ($n=26$), fever episodes ($n=3$), and unk ($n=25$). The grade of IE was 1 ($n=19$), 2 ($n=20$), 3($n=6$), 4 ($n=3$), 5 ($n=3$) and UNK ($n=29$). The time to IE was 48 days (7-161) and the number of Dara-2 4.

The median time to infection onset was 48 days (range 7–161), and patients had received a median of 4 Dara-RD cycles at the time of infection. The median duration of infection was 14 days (range 7–23). The immunoglobulin level at the time of IE was: IgG 238 (range 6-347), IgA 8(range 0–32) and IgM 5 (range 0–15). The WBC count at time of IE was 1490 (4-3585) and absolute neutrophil count was 1×10^9/L (4-1.8).

Cohort dara-VTD

We reviewed clinical data from 48 NDMM patients who developed infectious events (IEs) during treatment with the Daratumumab–Bortezomib–Thalidomide–Dexamethasone

Table 2 Type of infection and prophylaxis in three cohort

	Cohort Dara -RD 80 infections	Cohort Dara -VTD 48 infections	Cohort Dara-VMP 20 infections	*p*
Type of Infection, n (%)	26(20.8%)	15 (31.5%)	1(5%)	
	26(20.8%)	15 (31.5%)	0	
Pneumonia	3(3.7%)	2 (%)	0	
Fever	16(20%)	5 (10.1%)	3(15%)	
CMV				
Covid +				
Prophilaxis, n (%)	57(71.2%)	29(60.4%)	13(65%)	0.4
Bactrim	58(72.5%)	29 (60.4%)	14(70%)	
Aciclovir				

(Dara-VTD) regimen. Baseline characteristics of this cohort are summarized in Table 1.

At diagnosis, the median age was 62 years (range 57–67). The majority of patients were male (35/48), with 13 females. The ISS stage at diagnosis was: stage I ($n=14$), stage II ($n=8$), stage III ($n=5$), and unknown in 21 patients. Regarding fitness status, 29 patients were classified as fit; data were unavailable for the remaining 19 patients.

The median haemoglobin (Hb) level was 11.5 g/dL (10.7-13.15), β2m 3.3 mg/dL (2.1–5.3), median CM was 2.2 g/dL (1.−4.9), LDH were 157 (132–209). The WBC medium was 3.8×10^9/L (range 7-6.5), neutrophil count was 4.1×10^9/L (range 2-6.2) and absolute lymphocyte count was 1.4×10^9/L (range $0.6–2.2\times10^9$/L). The Ig dosage at diagnosis was: IgG 56 (range 32–883), IgA 1 (range 0–14) and IgM 0 (range 0–5). Cytogenetic testing was available for 45 of 48 patients (93%), with 8 of 48 (16%) classified as high-risk cytogenetic profiles.

The most common comorbidities at baseline were arterial hypertension ($n=9$), cardiomyopathy ($n=5$), and diabetes mellitus ($n=1$). Antiviral prophylaxis with acyclovir and antibacterial prophylaxis were administered in 29 of 48 patients (60%) each.

Details regarding the number, type, and severity of infectious events are presented in Table 2. Types of infections included: covid infection ($n=5$), cmv reactivation ($n=2$), pneumoniae ($n=15$), fever episodes ($n=3$), and unk ($n=19$). The grade of IE was 1 ($n=10$), 2 ($n=8$), 3($n=9$), 4 ($n=1$) and UNK ($n=20$). The time to IE onset was 59 days (18–147) and the median number of Dara-VTD cycles was 3 (range 2–4) The duration of IE was 14 (9–26) days. The median duration of IE was 14 (7–23) days. The Ig level at the time of IE was: IgG 178 (5-492), IgA 5 (0–19) and IgM 6 (0–12). The WBC count at time of IE was 2460 (8-5530) and absolute neutrophil count was 1.3×10^9/L (range $8\text{-}3.6\times10^9$/L).

Comparison between the three cohorts

Tables 1 and 2 summarize the baseline characteristics and infectious event (IE) data for the entire patient population. At baseline, statistically significant differences were observed between the Dara-VTD cohort (Cohort C) and the other two cohorts in terms of age and fitness status, as expected for a transplant-eligible (TE) population.

In addition, patients in Cohort B (Dara-RD) had a significantly lower median nadir absolute neutrophil count (ANC) compared to the other two cohorts (median 3.0×10^9/L, range $1.0–5.1\times10^9$/L; $p=0.043$). Patients in Cohort C (Dara-VTD) also showed significantly lower baseline immunoglobulin levels: IgG=p 0.025; IgA=$p<0.001$; IgM=p 0.004 (Figs. 1 and 2).

The type of prophylaxis and infectious events is reported in Table 2. The time to onset of IE differed significantly between TE and non-transplant-eligible (NTE) patients: 48 days in Cohorts A and B, versus 59 days in Cohort C ($p<0.001$). However, no significant differences were found among the three groups in terms of IE severity or duration.

Across all cohorts, a statistically significant reduction in IgA levels was observed at the time of infection compared to baseline ($p=0.006$), while IgG and IgM levels remained unchanged. Additionally, significant changes in neutropenia ($p=0.002$) and lymphocytopenia ($p=0.006$) were observed when comparing values before and after IE in all three groups.

The median progression-free survival (PFS) at 24 months was 68.3% (95% CI: 54.7–85.4; Fig. 1). Conversely, overall survival (OS) at 12 and 24 months did not significantly differ between the three cohorts ($p=0.13$; Fig. 3).

Among patients with available data, acyclovir prophylaxis was administered in 100% of cases and cotrimoxazole in 97%. However, data on prophylaxis were missing for approximately one-third of patients.

Discussion

The treatment of multiple myeloma (MM) has evolved significantly with the introduction of CD38-targeting agents. CD38 is a transmembrane glycoprotein that is highly expressed on MM cells and, to a lesser extent, on normal lymphoid and myeloid cells, as well as some non-hematopoietic tissues. Its high expression on MM cells makes CD38 an attractive therapeutic target. However, CD38 is also highly expressed on natural killer (NK) cells, and daratumumab—a CD38-directed monoclonal antibody—has been shown to deplete the NK cell compartment. Previous studies have demonstrated that NK cell decline can occur rapidly, early in the course of therapy. In animal models, NK cell impairment or depletion is associated with increased susceptibility to viral infections.

Despite substantial therapeutic advances over the past two decades that have significantly improved MM patient survival, infections remain a leading cause of morbidity and early mortality. The risk of infection in MM is

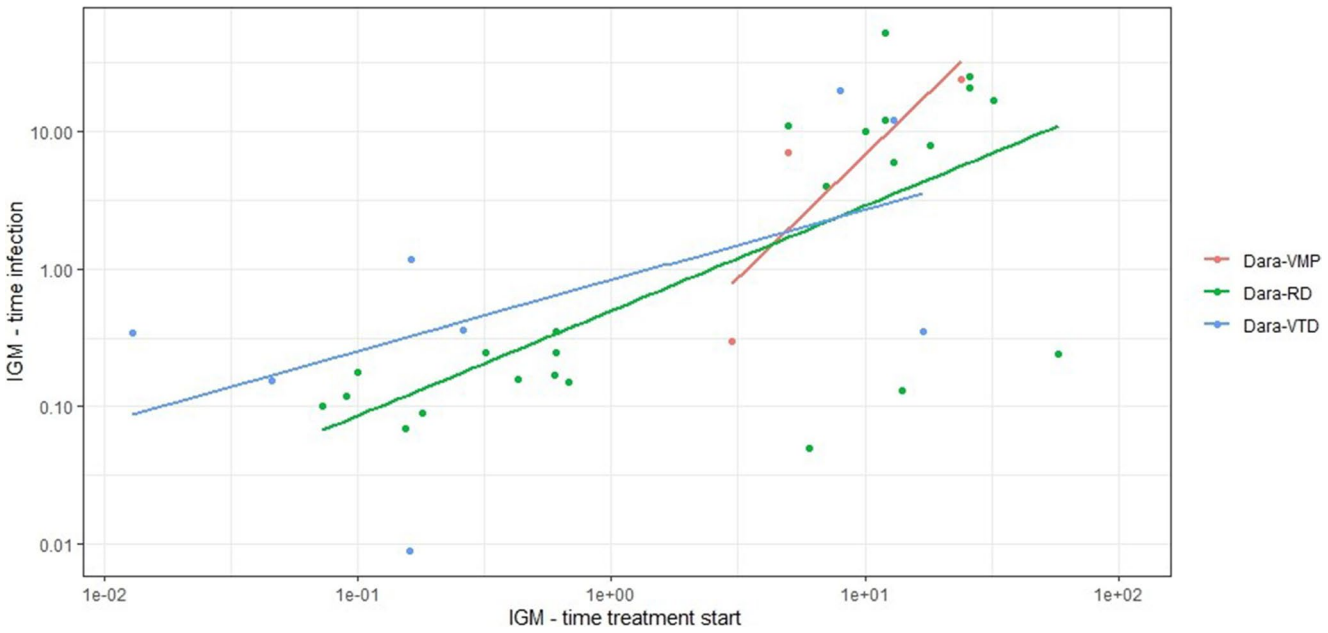

Fig. 1 IgM at time of infection in 3 groups

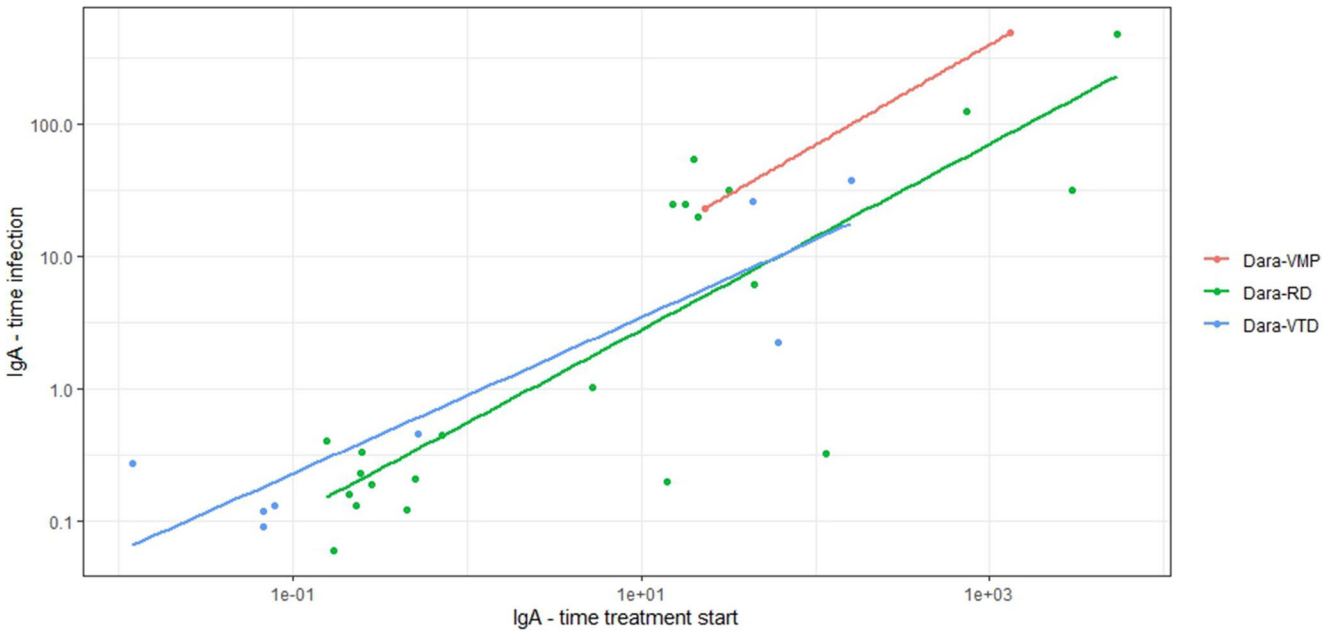

Fig. 2 IgA at time of infection in 3 groups

multifactorial and influenced by disease-related immunoparesis, patient comorbidities, and treatment-related immune suppression. Severe infections are most common during the initial months following diagnosis. Infection patterns have evolved alongside changing treatment strategies, including the use of proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), and anti-CD38 monoclonal antibodies.

Our study is the first to estimate the comparative risk and types of infectious events (IEs) associated with daratumumab during induction therapy in both transplant-eligible and -ineligible patients with newly diagnosed multiple myeloma (NDMM) treated with daratumumab-based combinations in a real-world setting. A major limitation of this study is its retrospective nature and the absence of a control cohort not exposed to daratumumab.

Among 472 NDMM patients treated with daratumumab-based regimens, we retrospectively analyzed the subset of 148 patients who experienced at least one infectious complication during treatment. Since some patients experienced multiple infections, the total number of infection

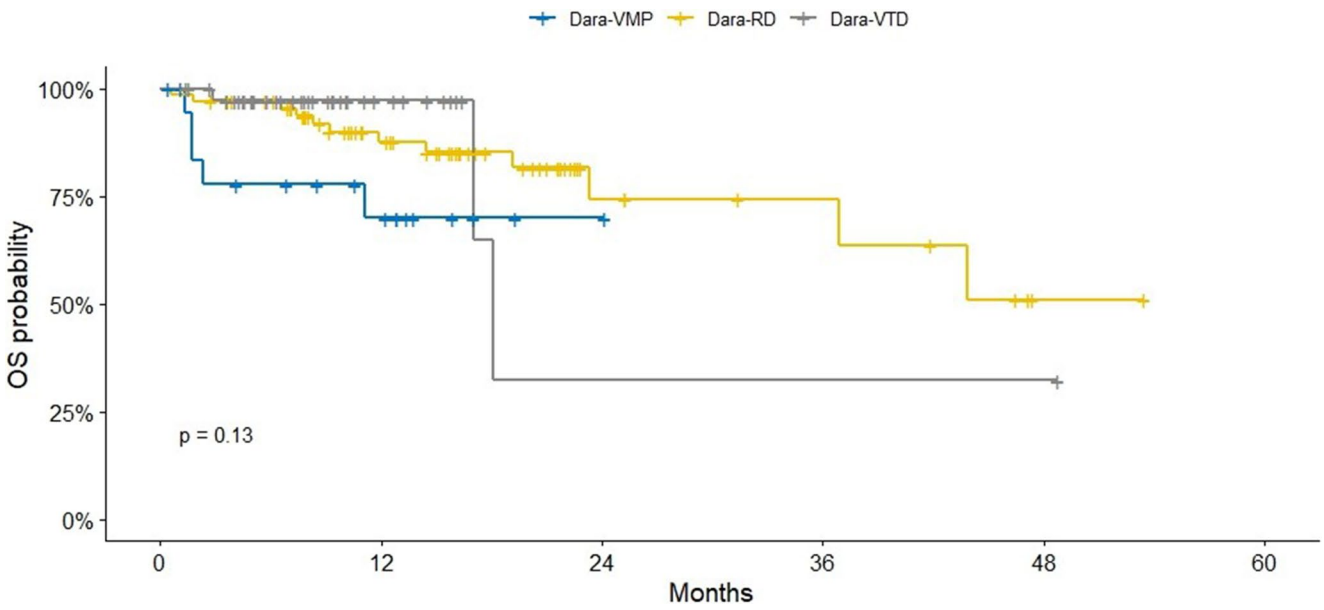

Fig. 3 Overall survival in 3 treatment group

events exceeded the number of patients analyzed. All 472 patients received one of the following regimens as induction therapy between 2020 and 2023: Dara-VTD, Dara-RD, or Dara-VMP. Of these, 148 patients developed an infection of any grade, which corresponds to an overall infection rate of 38%—a figure comparable to those previously reported in MM induction studies. Upper respiratory tract infections were the most common, though our observed rate was slightly lower than in some earlier reports.

A meta-analysis of five phase III randomized trials found that adding daratumumab to standard regimens increased the incidence of all-grade infections (risk ratio [RR] 1.27) and any-grade pneumonia (RR 1.63). While several studies suggest that prophylactic antibiotics or vaccinations before starting MM therapy can reduce the frequency and severity of early infections, their use remains inconsistent and somewhat controversial.

In our cohort, antimicrobial and antiviral prophylaxis was neither mandated nor standardized across participating centers. Instead, prophylaxis was administered at the discretion of individual treating physicians, leading to variability in practice. No significant differences in the use of antiviral or antimicrobial prophylaxis were observed among the three treatment groups.

The median time to the onset of infection was similar across regimens: 161 days (range 104–243) for Dara-VMP, 157 days (97–370) for Dara-RD, and 82 days (44–184) for Dara-VTD ($p=0.064$). Infectious events included upper respiratory tract infections (77%), COVID-19 (11%), herpes simplex and varicella-zoster virus infections (1.9%), abdominal infections (2.8%), and urinary tract infections (1.9%), with all grades combined. No differences in infection grade or duration were noted across treatment arms.

We conducted a comprehensive evaluation of infection risk in patients treated with daratumumab, aiming to identify predictors of infection to guide risk stratification and inform prophylaxis strategies. While no significant differences in infection incidence, type, or severity were found between treatment groups, we observed that low baseline immunoglobulin A (IgA) and M (IgM) levels, neutropenia, and lymphopenia at the time of infection were significantly associated with a higher infection risk. This supports the hypothesis that infection susceptibility is driven by neutropenia, hypogammaglobulinemia, and NK cell depletion.

The risk of neutropenia varies with the specific daratumumab regimen. Combination regimens—especially Dara-RD—are associated with higher rates of neutropenia (28–48%). Lymphopenia, a well-established risk factor for infections in MM, occurs at grade 3 or 4 severity in 3–6% of patients receiving IMiDs or bortezomib. Persistent and severe lymphopenia during daratumumab-based therapy is not uncommon and correlates with an increased risk of serious infections and poorer outcomes in some patient subsets. Thus, close monitoring and appropriate prophylactic interventions are warranted, particularly in patients with pre-existing lymphopenia.

In our experience, the addition of daratumumab during induction did not significantly increase the number, severity, or duration of infectious events across the three regimens, although a non-significant trend toward earlier infection onset was observed in the Dara-VTD group. This may be related to the use of quadruplet therapy versus triplet regimens (dara-rd and dara-vmp).

We observed significant changes in IgA, IgM, neutropenia, and lymphopenia before and after infection across all treatment groups. However, due to the limited sample size and incomplete data, we could not perform a multivariable analysis. Nonetheless, univariate analysis identified neutropenia, lymphopenia, and low baseline IgA and IgM levels as key infection risk factors—consistent with existing literature and reinforcing the role of baseline immune dysfunction in infection susceptibility during daratumumab-based therapy.

Larger, prospective studies are needed to validate these findings and to assess the efficacy of tailored prophylactic strategies across different daratumumab-containing regimens. In light of emerging induction therapies, future studies should also include comparative cohorts of daratumumab-naïve patients. Long-term follow-up and real-world data from registries will be essential to identify high-risk patients and clarify the clinical benefit of targeted prophylaxis in NDMM patients treated with daratumumab combinations.

Author contributions Angela Rago and Tommaso Caravita di Toritto wrote the manuscript. Alfonso Piciocchi analized the data. Luca Franceschini and Sonia More and Massimo Offidani and Elena Rossi and Stefano Pulini and Carmine Liberatore and Alessia Fiorini and Francesca Fazio and Tommaso Za and and Laura De Padua and Valeria. Tomarchio and Maria Antonietta Tafuri and Ombretta Annibali and Francesca Fioritoni and Francesca Di Landro collect the data. Maria Teresa Petrucci and Valerio De Stefano reviewed the manuscript.

Data availability No datasets were generated or analysed during the current study.

Declarations

Consent to participate statement andethical approval was obtained from a named committee (Comitato Etico Lazio 1) and that informed consent was received from all participants accordance with the Declaration of Helsinki.

Competing interests The authors declare no competing interests.

References

1. Palumbo A, Bringhen S, Ludwig H, Dimopoulos MA, Bladé J, Mateos MV, Rosiñol L, Boccadoro M, Cavo M, Lokhorst H, Zweegman S, Terpos E, Davies F, Driessen C, Gimsing P, Gramatzki M, Hàjek R, Johnsen HE, Leal Da Costa F, Sezer O, Spencer A, Beksac M, Morgan G, Einsele H, San Miguel JF, Sonneveld P (2011) Personalized therapy in multiple myeloma according to patient age and vulnerability: a report of the European myeloma network (EMN). Blood 118:4519–4529
2. Attal M, Harousseau JL, Stoppa AM, Sotto JJ, Fuzibet JG, Rossi JF, Casassus P, Maisonneuve H, Facon T, Ifrah N, Payen C, Bataille R (1996) A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. Intergroupe Français du Myélome. N Engl J Med 11:335:91–97
3. Encinas C, Hernadez-Rivas JA, Oriol A B, García-Sanz R6, De La Rubia J López De La Guía A, Jímenez-Ubieto A, Jarque I, Iñigo B, Dourdil V, De Arriba F, Cuéllar Pérez-Ávila C, Gonzalez Y, Hernández TM, Bargay J, Granell M, Rodríguez-Otero P, Silvent M, Cabrera C, Rios R, Alegre A, Gironella M, Gonzalez MS, Sureda A, Sampol A,Ocio E M, Krsnik I, García A, García-Mateo A, Soler JA, Martín J, Arguiñano JM, Mateos MV, Bladé J, San-Miguel JF, Lahuerta JJ, Martínez-López J (2022) GEM/PETHEMA (Grupo Español De Mieloma/Programa Para El Estudio De La Terapéutica En Hemopatías Malignas) Coop Study Group Simple Score Predict Early Severe Infections Patients New Diagnosed Multiple Myeloma Blood Cancer 12:68
4. Blimark C, Holmberg E, Mellqvist U-H, Landgren O, Björkholm M, Hultcrantz M, Kjellander C, Turesson Ingemar, Kristinsson Sigurdur Y (2015) Multiple myeloma and infections: a population-based study on 9253 multiple myeloma patients. Haematologica 100:107–13
5. Nucci M, Anaissie E (2009) Infections in patients with multiple myeloma in the era of high-dose therapy and novel agents. Clin Infect Dis 49:1211–1225
6. Caro J, Braunstein M, Williams L, Bruno B, Kaminetzky D, Siegel A, Razzo B, Alfanari S, Gareth J, Morgan, Davies FE, Boyle EM (2022) Inflammation and infection in plasma cell disorders: how pathogens shape the fate of patients leukemia. 36:613–624
7. Facon T, Kumar SK, Plesner T, Orlowski RZ, Moreau P, Bahlis N, Basu S, Nahi H, Hulin C, Quach H, Goldschmidt H, O'dwyer M, Perrot A, Venner CP, Weisel K, Mace JR, Raje N, Tiab M, Macro M, Frenzel F, Leleu X, Ahmadi T, Wang J, Rampelbergh RV, Uhlar CM,Tromp B, Delioukina M, Vermeulen J, Usmani SZ (2021) Daratumumab lenalidomide dexamethasone versus lenalidomide dexamethasone alone new diagnosed multiple myeloma (MAIA): Overall survival results randomised open-label phase 3 trial lancet oncol 22:1582–1596
8. Bahlis NJ, Dimopoulos MA, White DJ, Benboubker L, Cook G, Leiba M, Ho PJ, Kim K, Takezako N, Moreau P, Kaufman JL,Krevvata M, Chiu C, Qin X, Okonkwo L, Trivedi S, Ukropec J, Qi M, Miguel JS(2020) Daratumumab Plus Lenalidomide Dexamethasone relapsed/refractory Multiple Myeloma: Ext follow-up POLLUX Randomized open-label Phase 3. Study Leuk 34:1875–1884
9. Vassilopoulos S, Vassilopoulos A, Kalligeros M, Shehadeh F, Mylonakis E (2022) Cumulative incidence and relative risk of infection in patients with multiple myeloma treated with anti-cd38 monoclonal antibody-based regimens: a systematic review and meta-analysis. Open Forum Infect Dis 31;9(11)

10. Yanaba K, Yoshizaki A, Muroi E, Hara T, Ogawa F, Shimizu K, Sato S (2010) The proteasome inhibitor bortezomib inhibits T cell-dependent inflammatory responses. J Leukoc Biol Jul 88(1):117–122
11. Quach H, Ritchie D, Stewart AK, Neeson P, Harrison S, Smyth MJ, Prince HM (2009) Mechanism of action of immunomodulatory drugs (IMiDS) in multiple myeloma Leukemia. 12;24:22–32
12. Raza S, Safyan RA, Lentzsch S (2017) Immunomodulatory drugs (IMiDs) in multiple myeloma. Curr Cancer Drug Target 17:846–857
13. Colley A, Brauns T, Sluder AE, Poznansky MC, Gemechu Y (2024) Immunomodulatory drugs: a promising clinical ally for cancer immunotherapy. Trends Molecl Medicine 30(8):765–780
14. Li W, Liang L, Liao Q, Li Y, Zhou Y (2022) CD38: An important regulator of t cell function. Biomed Pharmacother 153:113395
15. Lakshman A, Rajkumar SV, Buadi FK, Binder M, Gertz MA, Lacy MQ, Dispenzieri A, Dingli D, Fonder AL, Hayman SR, Hobbs MA, Gonsalves WI, Hwa YL, Kapoor P, Leung N, Go RS, Lin Y, Kourelis TV, Warsame R, Lust JA, Russell SJ, Zeldenrust SR, Kyle RA, Kumar SK (2018) Risk stratification of smoldering multiple myeloma incorporating revised IMWG diagnostic criteria. Blood Cancer J 12(6):59
16. Gahagan A, Maheshwari S, Rangarajan S, Ubersax C, Tucker A, Harmon C, Pasala MS, Bal S, Godby K, Ravi G, Costa LJ, Williams GR, Bhatia S, Giri SJ (2024) Evaluating concordance between international myeloma working group (IMWG) frailty score and simplified frailty scale among older adults with multiple myeloma. J Geriatr Oncol 15:102051
17. Lim C, Sinha P, Harrison SJ, Quach H, Slavin MA, Teh BW (2021) Epidemiology and risks of infections in patients with multiple myeloma managed with new generation therapies. Clin Lymphoma Myeloma Leu 21:444–450
18. World Health Organization 's International Statistical Classification of Diseases–10th Revision (ICD-10)