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Effect of intravenous immunoglobulin on infections in multiple myeloma patients receiving daratumumab

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Contributions : GL designed the study and wrote the manuscript
DS and MA collected data and reviewed the manuscript
EM conducted statistical analyses
HJC, SJ, SP, SR, JR, CR, AR, LS, ST reviewed the manuscript
AC supervised the study and reviewed the manuscript

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Abstract:

Daratumumab is an anti-CD38 monoclonal antibody that has shown clinical benefit in both relapsed/refractory as well as newly diagnosed multiple myeloma (MM). Although daratumumab is very well-tolerated, randomized clinical trial data have consistently demonstrated an increased risk of infection, particularly along the respiratory tract, in patients receiving daratumumab. CD38 is present on healthy plasma cells, and their destruction can lead to hypogammaglobulinemia (HGG). In this study, we retrospectively reviewed all patients with MM treated with daratumumab and intravenous immunoglobulin (IVIG) at our institution from 2015-2019. The primary endpoints were the incidence rate ratios (IRR) of all-grade infections and grade 3-4 infections per patient-year during IVIG versus observation. In addition, a separate reference group of MM patients who were treated with daratumumab but never received IVIG was identified to establish baseline infection rates and to identify differences in baseline characteristics among patients who were selected to receive IVIG. A total of 43 patients received daratumumab and IVIG, primarily in the relapsed/refractory setting. All patients had HGG during treatment with daratumumab, with most (81%) experiencing moderate HGG (IgG <400mg/dL). During periods of IVIG use, all-grade infections were 43% lower and grade 3-4 infections were 70% lower compared to observation periods (no IVIG use). The reference group that had never received IVIG (n=100) had fewer infections in the year prior to daratumumab and a lower infection rate while on daratumumab. In conclusion, selected patients with multiple recurrent infections prior to starting daratumumab derived substantial benefit from the use of IVIG.

Introduction

Daratumumab is an anti-CD38 monoclonal antibody that has been shown to prolong progression-free survival (PFS) and overall survival (OS) for multiple myeloma (MM) patients in the relapsed/refractory and newly diagnosed settings.[1-9] Although daratumumab has relatively few toxicities and is generally very well tolerated, infection rates in patients enrolled in daratumumab-containing arms of randomized clinical trials are consistently higher than in the control arms. More frequently, these infections involve the respiratory tract .[10] Neutropenia and lymphopenia are known side effects of daratumumab and can be exacerbated when used in combination with immunomodulatory drugs (IMiDs). Nevertheless, the rates of febrile neutropenia are still quite low and likely not sufficient to explain the added infection risk.

Daratumumab targets CD38 on myeloma cells but also on healthy plasma cells, leading to hypogammaglobulinemia (HGG) in a significant proportion of patients.[11,12] HGG increases risk of infection with encapsulated organisms like *Haemophilus influenzae* and *Streptococcus pneumoniae*.[13,14] Intravenous immunoglobulin (IVIG) has been shown to reduce infections in multiple myeloma patients with HGG and well-controlled disease while receiving therapy with immunomodulatory drugs (IMiDs) and proteasome inhibitors (PIs),[15] as well as when patients are experiencing HGG due to to therapy with B-cell maturation antigen (BCMA)- targeting bispecific antibodies.[16,17]

This retrospective study is the first to evaluate the impact of IVIG on infection rates in daratumumab-treated MM patients by comparing infection rates of these patients 'on IVIG' treatment periods versus observation periods. In addition to the main study cohort, we also identified a reference group of MM patients who were treated with daratumumab but never received IVIG, in order to characterize baseline infection rates and to better understand patient selection for IVIG.

Methods

Study design and patient selection

This study consists of two main components. Part one is a retrospective crossover study including daratumumab-treated MM patients who received IVIG, and comparing rates of infections during periods of IVIG use vs periods of observation. We retrospectively identified all patients at the Tisch Cancer Institute at Mount Sinai from 2015-2019 with MM who were treated with daratumumab and had received at least one dose of IVIG while on daratumumab, There were no other exclusion criteria. This study period began at the date of first daratumumab administration and ended thirty days after the last daratumumab treatment. Patients were selected to receive IVIG at the discretion of their treating physician; although there were no uniform criteria for using IVIG, most physicians administered IVIG to patients who had HGG and recurrent infections, who were perceived to be at high risk for further infections.

In part two, we sought to identify a reference group of MM patients who were treated with daratumumab but never received IVIG, in order to establish baseline infection rates in this population and to understand differences in baseline characteristics among patients receiving and not receiving IVIG. A sample size of 100 patients had 80% power at an alpha of 0.05 to detect one fewer infection per patient-year than in the IVIG study group. These patients were selected at random from the total population of multiple myeloma patients receiving daratumumab at Mount Sinai during the same time period excluding those who received IVIG and those who received daratumumab for fewer than 3 months. We compared baseline characteristics to better understand factors leading to IVIG use, and for this reason there was no matching of baseline characteristics between these groups. Infections rates for this reference group are descriptive to contextualize the infection rates in the IVIG group but are not compared directly.

The study was approved by the Institutional Review Board of the Icahn School of Medicine at Mount Sinai.

Data collection and definitions

We collected data on baseline patient characteristics, MM history and treatment, immunoglobulin levels, use of IVIG, and infections. Infections were identified from microbiological data, anti-microbial prescriptions, and clinical documentation of infections. Infections were categorized as bacterial, viral, or fungal based on microbiological confirmation only. Relevant adverse events, including infections, neutropenia, and lymphopenia, were graded according to the Common Terminology Criteria for Adverse Events (CTCAE v4.0). HGG was defined as either IgG level below the lab reference range (<700mg/dL at our institution), or in the case of IgG myeloma, the M-spike was subtracted from the total IgG in order to account for the non-functional monoclonal component. Moderate HGG was defined as 200-<400 mg/dL, and severe HGG was <200mg/dL. IgG trough levels were measured to reflect the maximal severity of HGG. Additionally, IgG levels were collected at the time of infections. Infections occurring within 30 days after IVIG administration were classified as 'on IVIG', while the remainder occurred during observation periods. In part 1 of the study, patients were allowed to cross over multiple times between the IVIG and observation groups in the first part of the study. In part 2 of the study, all patients in the reference group were on observation only by definition .

Endpoints

The primary endpoints were the rates of all-grade infections and grade 3-4 infections, measured in infections per patient-year, during periods 'on IVIG' vs periods of observation in part one.

In part two, we sought to establish infection rates in patients who were not selected to receive IVIG, and to compare the baseline patient, disease, and treatment-related characteristics of this population with the IVIG population in part one. Key secondary endpoints for both parts were the rate and severity of HGG while on daratumumab, as well as rates of neutropenia and lymphopenia at the time of infections.

Statistical Analysis

The primary endpoints of all-grade and grade 3-4 infection rates 'on IVIG' vs observation were calculated using a self-controlled case series (SCCS) model,[18] with IVIG as the exposure and infection rates compared within patients, with patients serving as their own controls. Disease progression and seasonality were incorporated as time-varying covariates in sensitivity analyses. To evaluate potential indication bias, a pre-exposure risk period diagnostic was performed.[19,20] Pre-IVIG windows of 30 and 60 days before first IVIG were modeled as separate risk periods in the SCCS alongside on-IVIG and off-IVIG periods.

The secondary endpoints of proportions of Grade 3-4 and Grade 1-2 infections associated with neutropenia (defined as ANC≤0.5 or separately ANC≤1.0, both at time of infection) and/or lymphopenia(defined as ALC≤0.5 or separately ALC≤1.0, both at time of infection) in patients that were exposed to IVIG and in patients that were not exposed to IVIG are reported descriptively.

For patient-related and disease-related characteristics associated with IVIG use after daratumumab receipt, univariable Cox proportional hazards regression was used to identify potential risk factors for exposure to IVIG after daratumumab receipt with time-to-first IVIG receipt as the dependent variable. The proportional hazards assumption was assessed for violations. Hazard ratios with corresponding 95% confidence intervals and p-values are provided for each potential risk factor.

p-values less than 0.05 were considered statistically significant. Analyses were conducted using SAS statistical software.

Results

Part one- IVIG population

Patient characteristics

For part one of this study, of a total 1076 consecutive patients who received daratumumab, we identified 43 patients (4%) who received at least three doses of IVIG while being treated with daratumumab. Baseline characteristics are summarized in Table 1. Forty-four percent of these patients were female with a median age of 67 (range 37-86) at the start of daratumumab treatment. The proportion of patients with IgG myeloma was lower (40%) than expected for a standard MM population while the percentage of patients with light chain only myeloma was higher (37%). Patients were primarily treated with daratumumab in the relapsed setting, with a median of 2 prior lines (range 0-9) over 3.5 years (range 0-23.8) since initial diagnosis, with 46% having high-risk cytogenetics. Nearly all patients were previously exposed to a PI and IMiD (primarily bortezomib and lenalidomide), and just over half (56%) had prior autologous transplant. The most commonly used partner drugs with daratumumab in this study were pomalidomide (56%) and carfilzomib (40%), though regimens varied significantly both within and across patients, with many patients exposed to more than one regimen. No patients received daratumumab in combination with bispecific antibodies. Patients were on daratumumab for a

median of 21.1 months and had a median of 2 infections in the year prior to starting daratumumab. 42 (98%) patients were on antiviral prophylaxis, 6 (14%) were on antibacterial prophylaxis including fluoroquinolones or trimethoprim-sulfamethoxazole, and 5 (12%) were on antifungal prophylaxis. The overall response rate was 84% with a median time to first response of 1.3 months. Median OS from the time of first daratumumab dose was not reached; 5-year estimated OS was 61.6% (median OS from time of MM diagnosis was 9.2 years).

Infections

Forty-two patients (98%) experienced a total of 155 infections with a median time to first infection of 2.5 months. Infection rates by infection grade, type, and site among the "On-IVIG", "observation" and "reference" groups are presented in Figure 1**.** Most infections (55%) were in the respiratory tract, including 35% in the lower respiratory tract. Of the infections with microbiological confirmation, 43% were bacterial, 55% were viral, and 2% fungal. Twenty-three patients (53%) experienced infections classified as grade 3-4; no fatal infections were observed. Additionally, 12% of the infectious episodes occurred at the time of disease progression. Infection rates were similar in fall/winter months (1.76 per patient-year) and spring/summer months (1.59 per patient-year); IVIG was administered somewhat more frequently during fall/winter (43% of fall/winter person-time was on-IVIG) compared to spring/summer (36%).

At the time of infection, the median ANC was 3.0 $x10^3$/uL (range, 0-15.9) and median ALC was 1.0 $x10^3$/uL (range, 0-4.2). Grade 4 neutropenia (ANC <0.5 $x10^3$/uL) was present in 16.2% of grade 3-4 infections, while grade 3 lymphopenia (ALC <0.5 $x10^3$/uL) was present in 48.6% of grade 3-4 infections (Table 2).

Hypogammablobulinemia

Hypogammaglobulinemia (functional IgG <700mg/dL) was nearly universal (98%) during this study, with 79% experiencing at least moderate HGG (IgG< 400 mg/dL) and 19% with severe HGG (IgG< 200mg/dL) [Table 2]. Median functional IgG level was 566 mg/dL prior to daratumumab and 363 mg/dL at the time of starting IVIG. The median proportion of days on daratumumab that patients spent on IVIG was 37% however HGG was present 80% of the time.

Self-controlled case series showed that infection rates worsened with degree of HGG. Patients experienced higher infection rates during periods of any HGG (IgG <700mg/dL vs >700g/dL; IRR 1.56 [0.99, 2.44], p=0.0501), moderate HGG (IgG <400mg/dL vs >400g/dL; IRR 1.67 [1.14, 2.46], p=0.0085) and severe HGG (IgG <200mg/dL vs >200g/dL; IRR 3.07 [1.39, 6.80], p=0.0056).

Intravenous Immunoglobulin

Following a median of 3.2 months (range, 0-25.4) after the first dose of daratumumab, IVIG was administered to patients for a median of 7 months (range, 1-35) with a median of 7 (range, 1-43) IVIG doses received. IVIG was given intravenously at a dose of 0.4-0.5g/kg every 4 weeks. While

'On-IVIG', the all-grade infection rate was 43% lower compared with the observation periods, with 1.78 vs 3.10 infections per patient-year respectively (IRR 0.57, 95% CI [0.40-0.83], p=0.0035) [Figure 1]. With regards to grade 3-4 infections, the rate was 70% lower while 'On-IVIG' compared to observation periods (IRR 0.30, 95% CI [0.12-0.75], p=0.0101). Bacterial infections were reduced by 60% and viral infections were reduced by 31%, however these reductions were not statistically significant, probably due to the small sample size of microbiologically confirmed infections. A swimmer's plot showing the timing and grade of all infections divided by IVIG and observation periods is presented in Figure 2.

In a pre-exposure diagnostic analysis, the 30-day pre-IVIG period showed a non-significant trend toward higher infection rates (IRR 1.51, 95% CI 0.79-2.88, p=0.212), while the 60-day period was significantly elevated (IRR 2.40, 95% CI 1.50-3.84, p<0.001), consistent with infections prompting IVIG initiation. After adjusting for the pre-exposure period, the on-IVIG protective effect persisted (30-day: all-grade IRR 0.60, 95% CI 0.41-0.87, p=0.008; 60-day: all-grade IRR 0.68, 95% CI 0.46-1.00, p=0.053; grade 3+: IRR 0.38, 95% CI 0.14-0.99, p=0.049).

In a sensitivity analysis adjusting for disease progression as a time-varying covariate, the protective effect of IVIG remained unchanged (all-grade IRR 0.58 (0.40-0.84), p=0.004). Across fall/winter and spring/summer months, all-grade infection rates were lower during on-IVIG periods. In a sensitivity analysis adjusting for season as a time-varying covariate in the SCCS model, results were unchanged (all-grade IRR 0.57 (0.39-0.83), p=0.003).

Part two- Reference population

Patient characteristics, Hypogammaglobulinemia, and Infection Rates

Patient characteristics (demographic and disease specific) for the 100 randomly selected reference patients who received daratumumab but never received IVIG are listed in comparison to those of the IVIG population in Table 1. In general, the duration of daratumumab therapy in these patients was shorter compared to the IVIG group (median months on dara: 10.6 vs 21.1), In addition, these patients had fewer infections in the year prior to starting daratumumab. Interestingly, more patients had IgG myeloma, leading to a likely under-estimation of the HGG rates since nearly all patients experienced HGG (97%) once the monoclonal IgG component was factored in, just as in the IVIG group (98%). It is also important to note that patients in the reference group spent a larger proportion of their time on daratumumab with HGG compared to the IVIG group (88% vs 80%, p=0.0129), likely due to the therapeutic effect of IVIG on IgG numbers. Sixty-seven patients in this group (67%) had at least moderate HGG, and 19 patients (19%) had severe HGG.

Sixty-two patients (62%) experienced a total of 123 infections, with an annualized infection rate of 0.94. Sixteen patients (16%) experienced infections classified as grade 3-4 , with an annualized infection rate of 0.14; ,and none fatal. Most (81%) infection were in the respiratory tract, including 23% in the lower respiratory tract. Of the infections with microbiological confirmation, 31% were bacterial and 69% viral, with no fungal infections. Infection rates for infection subtypes are presented in Figure 1.

At the time of infection, the median ANC was 2.85 $x10^3$/uL (range, 0-42.7) and median ALC was 0.9 $x10^3$/uL (range, 0-4.7). Grade 4 neutropenia (ANC <0.5 $x10^3$/uL) was present 7.7% of grade 3-4 infections, while grade 3 lymphopenia (ALC <0.5 $x10^3$/uL) was present in 30.8% of grade 3-4 infections.

Risk factors for IVIG usage

Baseline characteristics were compared between the IVIG group and the reference group, to better understand patient selection to receive IVIG and to identify patients at higher perceived risk for infection that may benefit from IVIG (Table 1; Supplemental Table 1). Patients in the IVIG group had a higher median number of infections in the year prior to daratumumab initiation (2 vs 1; HR 1.87, 95% CI [1.40, 2.51], p< 0.0001), and were much more likely to have had 3 prior infections (HR 5.43, 95% CI [1.47, 20.03], p=0.0110) or 4+ prior infections (HR 15.24, 95% CI [4.65, 49.91], p<0.0001). Patients in the IVIG group were also significantly less likely to have IgG subtype myeloma (HR 0.19, 95% CI [0.08, 0.49], p=0.0005).

Discussion:

This is the first comprehensive study to date examining risk factors for infections and mitigation strategies, in particular use of IVIG, for MM patients receiving daratumumab. We found that in patients who were selected by their physician to receive IVIG, patients experienced a 43% lower risk of all-grade infection and 70% lower rate of grade 3-4 infections during 'on IVIG' periods compared to observation periods . Severe neutropenia (grade 3+) was relatively uncommon at the time of any-grade or grade 3-4 infections, whereas grade 3+lymphopenia was more common, occurring in 49% of grade 3-4infections. In the patient population who received IVIG, HGG was observed in all the patients during daratumumab treatment, with most (81%) patients experiencing moderate HGG (IgG <400mg/dL) and about 21% experiencing severe HGG (IgG < 200 mg/dL), with worsening HGG correlating with higher infection risk. One prior study found no difference in bacterial pneumonia rates in patients on anti-CD38 therapy with or without IVIG; however, granular data analyzing IVIG on/off periods, IVIG indication, functional HGG, and prior infection rates were not reported.[21] Furthermore, the utility of IVIG in preventing infections is not limited only to bacterial pneumonias.[22]

As patients in our study were selected to receive IVIG based on their physician's discretion, these patients were likely to be at higher perceived or actual risk of infection and may not have been representative of the broader daratumumab-treated population. Therefore, we included a reference group of 100 patients who had received daratumumab but never received IVIG to contextualize infection rates and to identify patients at higher perceived risk for infection who may benefit from IVIG. Per our observations, patients who were selected to receive IVIG had a higher median number of infections in the year prior to daratumumab receipt (2 vs 1), and were much more likely to have had 3 or 4+ prior infections. It is clear from the low rate of infections in

the reference group that not all patients treated with daratumumab require IVIG despite the fact that HGG was also a very common observation in this reference population. The absence of infectious deaths also explains the OS benefits associated with the addition of daratumumab in multiple phase 3 randomized clinical trials despite an increased risk of infections. Therefore, the single most important factor in deciding on IVIG usage while receiving treatment with daratumumab is recurrent infections in the year prior to daratumumab initiation.

While IVIG usage demonstrated substantial benefits in a population at high risk for infections, the increased infection risk due to daratumumab is multi factorial, including neutropenia, lymphopenia, depletion of NK cells, and disruption of macrophage and dendritic cell function [23-25]. In particular, we found that lymphopenia was present to a significant degree during infections, and in particular high-grade infections. Severe lymphopenia has previously been shown to be associated with severe infections in MM patients treated with daratumumab, although the exact mechanisms are yet to be elucidated.[26] Furthermore, multiple studies have correlated lymphopenia with worse outcomes from respiratory infections including COVID-19 and bacterial pneumonia.[27-29] The presence of lymphopenia in daratumumab-treated patients should be considered as a possible additional risk factor for serious infections. Future studies correlating detailed flow cytometry data on lymphocyte populations and with infections may help better define at-risk patients receiving daratumumab. Additionally, we did not perform functional T-cell assays or antibody responses to vaccines which can add further clarity to the capability of the endogenous immune response.

This study has important limitations. All patients except one in the IVIG group were treated in the relapsed setting, with prior lines of therapy ranging from 0 up to 9, most commonly in combination with carfilzomib or pomalidomide which could exacerbate the immune suppression in these patients as well. While the SCCS design controls for all time-invariant confounders, and we additionally adjusted for disease progression and seasonality as time-varying covariates with no material change in results, other time-varying factors such as changes in anti-myeloma therapy and cumulative immunosuppression were not explicitly modeled. The small sample size and multiple IVIG exposure transitions limited further time-varying stratification.

While these regimens remain relevant in the relapsed setting, the landscape in MM is evolving rapidly and now many countries are able to utilize anti-CD38 containing regimens as frontline therapy both for transplant-eligible and transplant-ineligible patients. With prolonged use of anti-CD38 antibodies during maintenance post-transplant and especially in older and/or frailer transplant ineligible patients it is becoming even more important to identify patients at high risk for infections early on in order to find the optimal risk/benefit ratio for IVIG use. IVIG carries its own well-known adverse effects, is expensive, and is in limited supply, therefore optimal patient selection is crucial. In addition, demand for IVIG among the MM population is now surging due to the use of primary prophylaxis for patients treated with anti-BCMA CAR-T and bispecific antibodies[30,31], further contributing to potential scarcities and future restrictions on use. Although the findings in this study cannot be directly translated to the newly diagnosed setting, they may serve as a starting point for future studies.

It is relevant to note this study was conducted prior to the COVID-19 pandemic, and treatment with anti-CD38 antibodies has been shown to lead to inferior outcomes with COVID-19 infection as well as decreased vaccine response.[32-35] Therefore, the infection risk profile may continue to evolve along with the trajectory of the COVID-19 pandemic. IVIG has the added benefit of delivering neutralizing SARS-CoV-2 antibodies given the high prevalence of vaccination and natural infection in the donor plasma pool.[36-38]

Although the relatively small sample size of this study may have precluded more granular findings on infection risk and mitigation, there was a very clear and robust reduction in all-grade infection and high-grade infections with IVIG in patients at high risk for infection. In addition, findings of this study also support that only a small subset of daratumumab-treated patients will require treatment with IVIG, and these appear to be patients with multiple recurrent infections in the year prior to starting daratumumab. Future studies will help elucidate the role of IVIG in MM patients treated with daratumumab in the frontline setting.

References

1. Mateos MV, Cavo M, Blade J, et al. Overall survival with daratumumab, bortezomib, melphalan, and prednisone in newly diagnosed multiple myeloma (ALCYONE): a randomised, open-label, phase 3 trial. Lancet. 2020;395(10218):132-141.
2. Facon T, Kumar SK, Plesner T, et al. Daratumumab, lenalidomide, and dexamethasone versus lenalidomide and dexamethasone alone in newly diagnosed multiple myeloma (MAIA): overall survival results from a randomised, open-label, phase 3 trial. Lancet Oncol. 2021;22(11):1582-1596.
3. Voorhees PM, Sborov DW, Laubach J, et al. Addition of daratumumab to lenalidomide, bortezomib, and dexamethasone for transplantation-eligible patients with newly diagnosed multiple myeloma (GRIFFIN): final analysis of an open-label, randomised, phase 2 trial. Lancet Haematol. 2023;10(10):e825-e837.
4. Sonneveld P, Chanan-Khan A, Weisel K, et al. Overall survival with daratumumab, bortezomib, and dexamethasone in previously treated multiple myeloma (CASTOR): a randomized, open-label, phase III trial. J Clin Oncol. 2023;41(8):1600-1609.
5. Dimopoulos MA, Oriol A, Nahi H, et al. Overall survival with daratumumab, lenalidomide, and dexamethasone in previously treated multiple myeloma (POLLUX): a randomized, open-label, phase III trial. J Clin Oncol. 2023;41(8):1590-1599.
6. Usmani SZ, Quach H, Mateos MV, et al. Final analysis of carfilzomib, dexamethasone, and daratumumab vs carfilzomib and dexamethasone in the CANDOR study. Blood Adv. 2023;7(14):3739-3748.
7. Dimopoulos MA, Terpos E, Boccadoro M, et al. Subcutaneous daratumumab plus pomalidomide and dexamethasone versus pomalidomide and dexamethasone in patients with relapsed or refractory multiple myeloma (APOLLO): extended follow up of an open-label, randomised, multicentre, phase 3 trial. Lancet Haematol. 2023;10(10):e813-e824.
8. Moreau P, Hulin C, Perrot A, et al. Bortezomib, thalidomide, and dexamethasone with or without daratumumab and followed by daratumumab maintenance or observation in transplant-eligible newly diagnosed multiple myeloma: long-term follow-up of the CASSIOPEIA randomised controlled phase 3 trial. Lancet Oncol. 2024;25(8):1003-1014.
9. Sonneveld P, Dimopoulos MA, Boccadoro M, et al. Daratumumab, Bortezomib, Lenalidomide, and Dexamethasone for Multiple Myeloma. N Engl J Med. 2024;390(4):301-313.
10. Vassilopoulos S, Vassilopoulos A, Kalligeros M, Shehadeh F, Mylonakis E. Cumulative incidence and relative risk of infection in patients with multiple myeloma treated tith anti-CD38 monoclonal antibody-based regimens: a systematic review and meta-analysis. Open Forum Infectious Diseases. 2022;9(11):ofac574.
11. Paul Y, Aguirre LE, Basher F, Miao F, Koru-Sengul T, Hoffman JE. Hypogammaglobulinemia and its implications in patients treated with daratumumab: a single institution experience. Blood. 2019;134(Supplement_1):3131.
12. Hong JS, Zhou B, Yee AJ, Barmettler S. Hypogammaglobulinemia and daratumumab in multiple myeloma: risk Ffactors, infections, immunoglobulin replacement, and mortality. Blood. 2024;144(Supplement 1):3353.
13. Saba HI, Hartmann RC, Herion JC. Hemophilus influenzae septicemia and polyarthritis in multiple myeloma. South Med J. 1979;72(6):743-746.

14. King K. Septicaemia in patients with haematological malignant disease. Med J Aust. 1980;1(12):603-606.
15. Lancman G, Lozada K, Athar N, et al. Efficacy of intravenous immunoglobulin for oreventing infections in patients with multiple myeloma. Clin Lymphoma Myeloma Leuk. 2021;21(5):e470-e476.
16. Lancman G, Parsa K, Kotlarz K, et al. IVIg Use associated with ten-fold reduction of serious infections in multiple myeloma patients treated with Anti-BCMA bispecific antibodies. Blood Cancer Discov. 2023;4(6):440-451.
17. Frerichs KA, Verkleij CPM, Mateos MV, et al. Teclistamab impairs humoral immunity in patients with heavily pretreated myeloma: importance of immunoglobulin supplementation. Blood Adv. 2024;8(1):194-206.
18. Whitaker HJ, Farrington CP, Spiessens B, Musonda P. Tutorial in biostatistics: the self-controlled case series method. Stat Med. 2006;25(10):1768-1797.
19. Whitaker HJ, Hocine MN, Farrington CP. The methodology of self-controlled case series studies. Stat Methods Med Res. 2009;18(1):7-26.
20. Requena G, Douglas IJ, Huerta C, de Abajo F. Impact of pre-exposure time bias in self-controlled case series when the event conditions the exposure: Hip/femur fracture and use of benzodiazepines as a case study. Pharmacoepidemiol Drug Saf. 2020;29(4):388-395.
21. Konieczny K, Eighmy W, Rux E, Yamartino K, Parker T. The utility of intravenous immunoglobulin infection prophylaxis in patients on anti-CD38 therapies. J Oncol Pharm Pract. 2025:10781552251347240.
22. Perez EE, Orange JS, Bonilla F, et al. Update on the use of immunoglobulin in human disease: A review of evidence. J Allergy Clin Immunol. 2017;139(3):S1-S46.
23. Johnson SK, Burke S, Henry M, et al. Characterization of the Immune Impact of Daratumumab By Mass Cytometry in Multiple Myeloma. Blood. 2018;132(Supplement 1):4466.
24. Casneuf T, Adams HC, van de Donk NWCJ, et al. Deep immune profiling of patients treated with lenalidomide and dexamethasone with or without daratumumab. Leukemia. 2021;35(2):573-584.
25. Glaría E, Valledor AF. Roles of CD38 in the Immune Response to Infection. Cells. 2020;9(1):228.
26. Cottini F, Huang Y, Williams N, et al. Real World Experience of Daratumumab: Evaluating Lymphopenia and Adverse Events in Multiple Myeloma Patients. Front Oncol. 2020;10:575168.
27. Zhao Q, Meng M, Kumar R, , et al. Lymphopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: A systemic review and meta-analysis. Int J Infect Dis. 2020;96:131-135.
28. Doeleman SE, Reijnders TDY, Joosten SCM, et al. Lymphopenia is associated with broad host response aberrations in community-acquired pneumonia. J Infect. 2024;88(4):106131.
29. Warny M, Helby J, Nordestgaard BG, Birgens H, Bojesen SE. Lymphopenia and risk of infection and infection-related death in 98,344 individuals from a prospective Danish population-based study. PLoS Med. 2018;15(11):e1002685.
30. Lin Y, Qiu L, Usmani S, et al. Consensus guidelines and recommendations for the management and response assessment of chimeric antigen receptor T-cell therapy in clinical practice for relapsed and refractory multiple myeloma: a report from the International Myeloma Working Group Immunotherapy Committee. Lancet Oncol. 2024;25(8):e374-e387.

31. Rodriguez-Otero P, Usmani S, Cohen AD, et al. International Myeloma Working Group immunotherapy committee consensus guidelines and recommendations for optimal use of T-cell-engaging bispecific antibodies in multiple myeloma. Lancet Oncol. 2024;25(5):e205-e216.
32. Jin D, He J, Wu W, et al. Outcomes of COVID-19 in multiple myeloma patients treated with daratumumab. Cancer Sci. 2024;115(1):237-246.
33. Henriquez S, Zerbit J, Bruel T, et al. Anti-CD38 therapy impairs SARS-CoV-2 vaccine response against alpha and delta variants in patients with multiple myeloma. Blood. 2022;139(6):942-946.
34. Van Oekelen O, Gleason CR, Agte S, et al. Highly variable SARS-CoV-2 spike antibody responses to two doses of COVID-19 RNA vaccination in patients with multiple myeloma. Cancer Cell. 2021;39(8):1028-1030.
35. Aleman A, Upadhyaya B, Tuballes K, et al. Variable cellular responses to SARS-CoV-2 in fully vaccinated patients with multiple myeloma. Cancer Cell. 2021;39(11):1442-1444.
36. Romero C, Díez J-M, Gajardo R. Anti-SARS-CoV-2 antibodies in healthy donor plasma pools and IVIG products—an update. Lancet Infect Dis. 2022;22(1):19.
37. Jordan SC, Berg A, Shin B, Vo A, Ammerman N, Zhang R. Intravenous immunoglobulin contains high-titer neutralizing IgG antibodies to SARS-CoV-2. Am J Transplant. 2022;22(10):2484-2485.
38. Upasani V, Townsend K, Wu MY, et al. Commercial Immunoglobulin Products Contain Neutralizing Antibodies Against Severe Acute Respiratory Syndrome Coronavirus 2 Spike Protein. Clin Infect Dis. 2023;77(7):950-960.

Tables and Figure Legends

Table 1: Baseline Characteristics with Univariable Cox Regression (Outcome: Time to First IVIG Receipt)

Characteristic	IVIG (N=43)	Reference (N=100)	HR (95% CI)	P-value
Age at dara, years, median (range)	66.9 (37.4-85.7)	67.4 (40.4-89.0)	1.03 (0.90-1.18) per 5 yr	0.640
Sex				
Male (ref)	24 (56%)	53 (53%)	Ref	
Female	19 (44%)	47 (47%)	0.89 (0.49-1.63)	0.715
Months on dara, median (range)	21.1 (3.0-60.9)	10.6 (3.2-45.8)	1.03 (1.00-1.05)	0.020
Years from dx to dara, median (range)	4.1 (0.3-14.8)	3.5 (0.0-23.8)	1.02 (0.71-1.48) per 5 yr	0.897
Lines of therapy, median (range)	2.0 (0.0-9.0)	2.0 (0.0-11.0)	1.02 (0.89-1.16)	0.776
Infections in year prior, median (range)	2.0 (0.0-6.0)	1.0 (0.0-4.0)	1.60 (1.32-1.94)	<0.001
Prior infections (categorized)				
0	7 (18%)	32 (34%)	Ref	
1	8 (20%)	39 (41%)	0.94 (0.34-2.59)	0.905
2	10 (25%)	15 (16%)	2.46 (0.93-6.47)	0.068
3	7 (18%)	6 (6%)	4.04 (1.41-11.57)	0.009
4+	8 (20%)	2 (2%)	6.31 (2.28-17.46)	<0.001
Heavy chain type				
None (light chain only) (ref)	16 (37%)	17 (17%)	Ref	
IgG	17 (40%)	66 (66%)	0.40 (0.20-0.79)	0.008
IgA	9 (21%)	16 (16%)	0.75 (0.33-1.71)	0.500
IgD	1 (2%)	1 (1%)	0.82 (0.11-6.22)	0.849
IgE	0 (0%)	0 (0%)		
IgM	0 (0%)	0 (0%)		
Light chain type				
Lambda	18 (42%)	30 (30%)	Ref	
Kappa	25 (58%)	70 (70%)	0.66 (0.36-1.20)	0.172
Both	0 (0%)	0 (0%)		
ISS stage				
I	12 (32%)	27 (40%)	Ref	
II	11 (29%)	18 (27%)	1.35 (0.59-3.07)	0.474
III	15 (39%)	22 (33%)	1.77 (0.82-3.79)	0.144
R-ISS stage				
I	5 (14%)	9 (15%)	Ref	
II	22 (63%)	38 (64%)	1.04 (0.39-2.75)	0.936
III	8 (23%)	12 (20%)	1.25 (0.41-3.83)	0.696
High-risk cytogenetics				
No	21 (54%)	50 (56%)	Ref	
Yes	18 (46%)	39 (44%)	1.17 (0.62-2.20)	0.627
HGG at baseline (IgG<700)				
No	12 (28%)	41 (41%)	Ref	
Yes	31 (72%)	59 (59%)	1.66 (0.85-3.24)	0.135

Characteristic	IVIG (N=43)	Reference (N=100)	HR (95% CI)	P-value
Severe HGG (IgG<400)				
No	27 (63%)	83 (83%)	Ref	
Yes	16 (37%)	17 (17%)	2.19 (1.18-4.08)	0.013

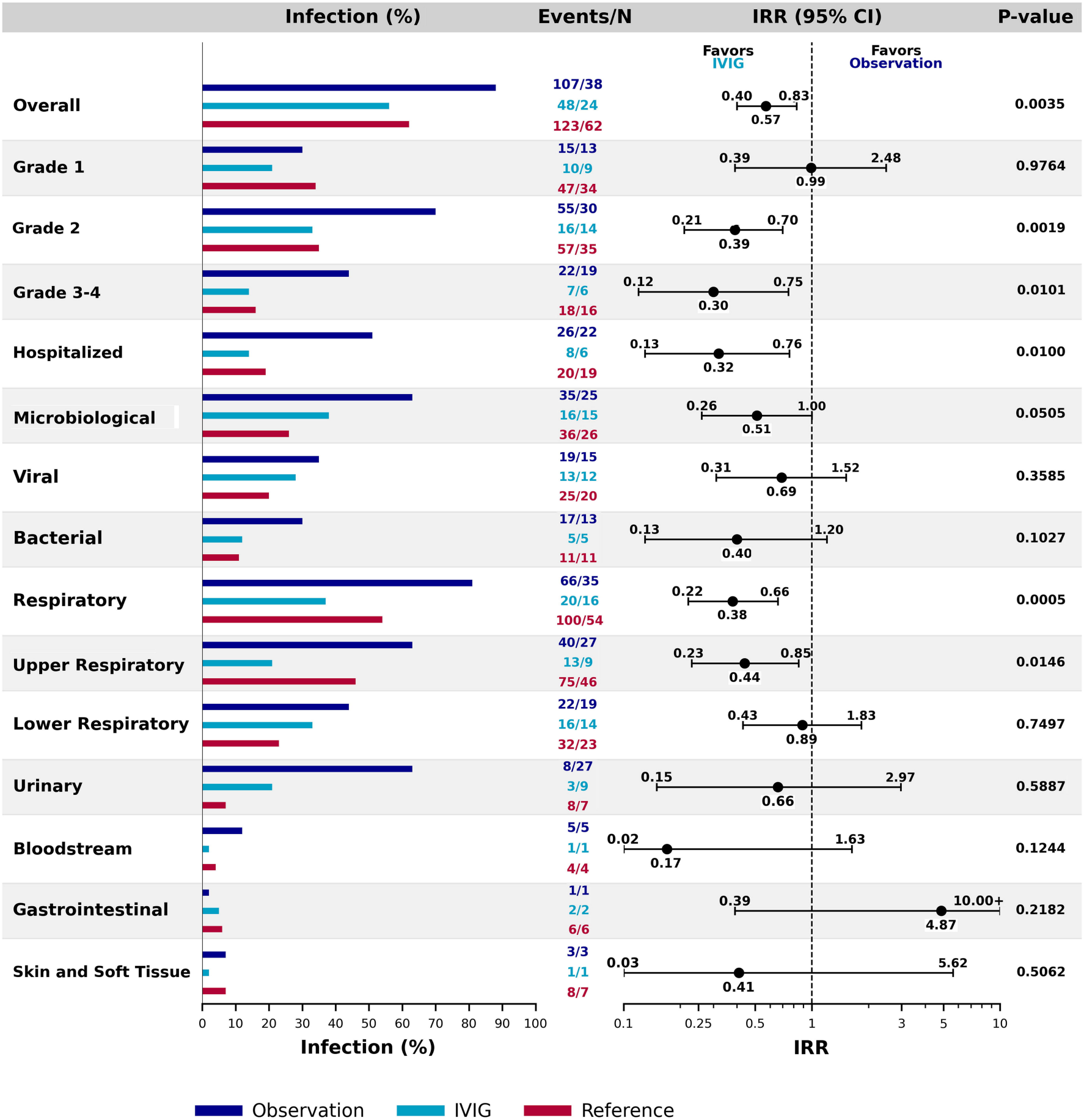
Note: Age and years from dx reported per 5-year increase. HGG derived from IgG levels within 90 days before to 10 days after first dara; M-spike subtracted for IgG-type myeloma.

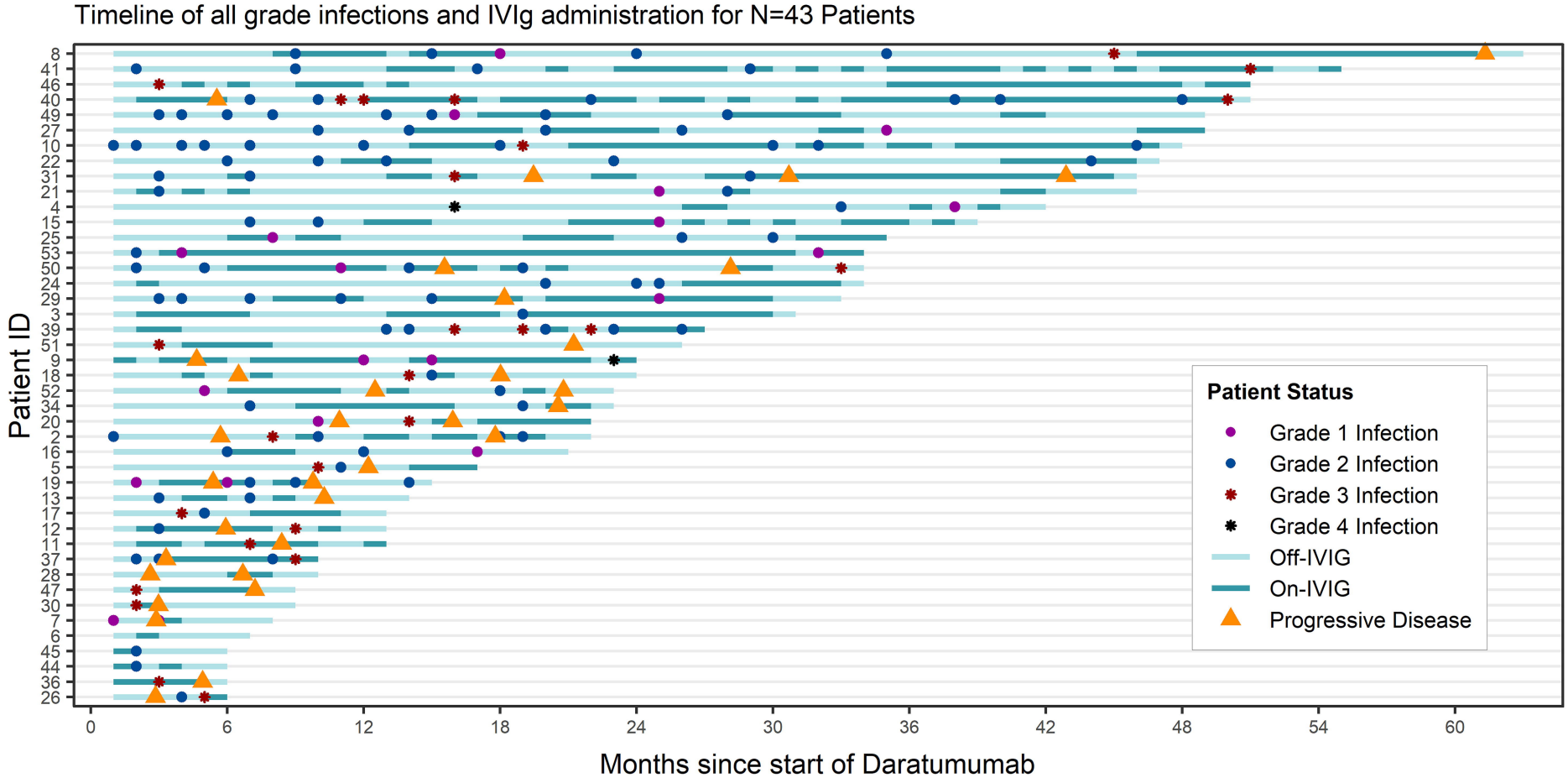
Table 2: Hypogammaglobulinemia, neutropenia, and lymphopenia in the IVIG group in part one (n=43)

Characteristic	
Hypogammaglobulinemia during study period, n(%) IgG < 700mg/dL IgG < 400mg/dL IgG < 200mg/dL	 42 (98%) 34 (79%) 8 (19%)
Functional IgG (mg/dL) prior to first daratumumab, median (range)	566 (115-1108)
Functional IgG (mg/dL) prior to first IVIG, median (range)	363 (200-1104)
Proportion of days 'On IVIG', median (range)	37% (8-93%)
Time (months) to first infection on daratumumab, median (range)	2.5 (0.1-18.7)
Absolute neutrophil count (ANC) $x10^3$/uL at time of infection, median (range) ANC < 0.5 $x10^3$/uL ANC < 1.0 $x10^3$/uL	3.0 (0-15.9) Grade 1/2: 2.2% Grade 3/4: 16.2% Grade 1/2: 5.0% Grade 3/4: 24.3%
Absolute lymphocyte count (ALC) $x10^3$/uL at time of infection, median (range) ALC < 0.5 $x10^3$/uL ALC < 1.0 $x10^3$/uL	29.0 (0-4.2) Grade 1/2: 13.7% Grade 3/4: 48.6% Grade 1/2: 43.9% Grade 3/4: 64.9%

Figure 1: Forest plot comparing incidence rate ratio of infections between periods of IVIG use and observation (n=43). The reference population is included to contextualize infection rates but is not compared statistically.

Figure 2: Swimmer's plot showing timing and grade of all infections divided by IVIG and observation periods


Infection (%)
Events/N
IRR (95% CI)
P-value
Favors IVIG
Favors Observation
Overall
107/38
48/24
123/62
0.40
0.83
0.57
0.0035
Grade 1
15/13
10/9
47/34
0.39
2.48
0.99
0.9764
Grade 2
55/30
16/14
57/35
0.21
0.70
0.39
0.0019
Grade 3-4
22/19
7/6
18/16
0.12
0.75
0.30
0.0101
Hospitalized
26/22
8/6
20/19
0.13
0.76
0.32
0.0100
Microbiological
35/25
16/15
36/26
0.26
1.00
0.51
0.0505
Viral
19/15
13/12
25/20
0.31
1.52
0.69
0.3585
Bacterial
17/13
5/5
11/11
0.13
1.20
0.40
0.1027
Respiratory
66/35
20/16
100/54
0.22
0.66
0.38
0.0005
Upper Respiratory
40/27
13/9
75/46
0.23
0.85
0.44
0.0146
Lower Respiratory
22/19
16/14
32/23
0.43
1.83
0.89
0.7497
Urinary
8/27
3/9
8/7
0.15
2.97
0.66
0.5887
Bloodstream
5/5
1/1
4/4
0.02
1.63
0.17
0.1244
Gastrointestinal
1/1
2/2
6/6
0.39
10.00+
4.87
0.2182
Skin and Soft Tissue
3/3
1/1
8/7
0.03
5.62
0.41
0.5062
0
10
20
30
40
50
60
70
80
90
100
Infection (%)
0.1
0.25
0.5
1
3
5
10
IRR
Observation
IVIG
Reference


Timeline of all grade infections and IVIg administration for N=43 Patients
Patient ID
8
41
46
40
49
27
10
22
31
21
4
15
25
53
50
24
29
3
39
51
9
18
52
34
20
2
16
5
19
13
17
12
11
37
28
47
30
7
6
45
44
36
26
0
6
12
18
24
30
36
42
48
54
60
Months since start of Daratumumab
Patient Status
Grade 1 Infection
Grade 2 Infection
Grade 3 Infection
Grade 4 Infection
Off-IVIG
On-IVIG
Progressive Disease

Supplementary Table 1: Multivariable Cox Regression comparing IVIG group and reference group

Variable	Adjusted HR	95% CI	P-value
Age (per 5 yr)	1.17	0.95-1.44	0.140
Years dx to dara (per 5 yr)	1.59	0.81-3.14	0.179
lines_of_therapy	0.84	0.66-1.07	0.167
numinfections	1.88	1.42-2.48	<0.001
Sex: Female	1.14	0.52-2.51	0.744
Heavy chain: IgG	0.24	0.10-0.59	0.002
Heavy chain: IgA	0.38	0.13-1.15	0.088
Heavy chain: IgD	6.22	0.49-78.43	0.157
Heavy chain: IgE	NA	NA-NA	NA
Heavy chain: IgM	NA	NA-NA	NA
Light chain: Kappa	1.50	0.61-3.65	0.378
Light chain: Both	NA	NA-NA	NA
ISS: II	1.95	0.76-4.98	0.162
ISS: III	1.99	0.80-4.98	0.140
High-risk cyto: Yes	1.01	0.44-2.32	0.974
HGG baseline: Yes	1.83	0.66-5.02	0.244

Reference groups: Sex=Male, Heavy chain=None (light chain only), Light chain=Lambda, ISS=I, High-risk cyto=No, HGG=No