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American Society of Hematology
2021 L Street NW, Suite 900,
Washington, DC 20036
Phone: 202-776-0544 | Fax 202-776-0545
bloodadvances@hematology.org

Prospective study of immunogenicity to SARS-CoV-2 booster vaccines in multiple myeloma and Waldenström macroglobulinemia

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Andrew Branagan (Massachusetts General Hospital, United States) Clifton Mo (Dana-Farber Cancer Institute, Harvard Medical School, United States) Matthew Lei (Massachusetts General Hospital Cancer Center, United States) Joshua Gustine (, United States) Andrew Yee (Massachusetts General Hospital Cancer Center, United States) Elizabeth O'Donnell (Massachusetts General Hospital,) Jorge Castillo (Dana-Farber Cancer Institute, United States) Omar Nadeem (Dana-Farber Cancer Institute, United States) Catherine Flynn (Dana Farber Cancer Institute, United States) Zachary Bernstein (Massachusetts General Hospital Cancer Center, United States) Rie Nakamoto-Matsubara (Massachusetts General Hospital Cancer Center, United States) Kirsten Meid (Dana Farber Cancer Institute, United States) Rakesh Verma (Massachusetts General Hospital, Harvard Medical School, United States) Zachary Hunter (Dana Farber Cancer Institute, United States) Maria Luisa Guerrera (Dana Farber Cancer Institute, United States) Galit Alter (Ragon Institute of Mass General, MIT, and Harvard, United States) Jill Burke (Massachusetts General Hospital Cancer Center, United States) Cynthia Harrington (Massachusetts General Hospital Cancer Center, United States) Emerentia Agyemang (Massachusetts General Hospital, United States) Marilyn Gammon (Massachusetts General Hospital Cancer Center, United States) Kathleen Lively (Massachusetts General Hospital Cancer Center, United States) Lisette Packer (Massachusetts General Hospital Cancer Center, United States) Nora Horick (Massachusetts General Hospital, United States) Jacob Laubach (Dana-Farber Cancer Institute, United States) Constantine Mitsiades (Dana-Farber Cancer Institute, Harvard Med. School, United States) Nikhil Munshi (Dana Farber Cancer Institute, United States) Kenneth Anderson (Dana-Farber Cancer Institute, United States) Steven Treon (Dana Farber Cancer Institute, United States) Paul Richardson (Dana-Farber Cancer Institute, Harvard Medical School, United States) Noopur Raje (Massachusetts General Hospital, United States) Shayna Sarosiek (Dana Farber Cancer Institute, United States)

Abstract:
Patients with multiple myeloma (MM) and Waldenström macroglobulinemia (WM) have increased risk of severe COVID-19. Impaired humoral responses to the primary vaccination series against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been reported in MM and WM patients, but impact of booster vaccinations and functional status of the elicited antibodies is unknown. We performed a prospective cohort study investigating SARS-CoV-2 vaccination in MM (n=93) and WM (n=48) patients. The primary endpoint was effective immune response (EIR) at 28 days after the primary vaccination series (i.e., anti-spike SARS-CoV-2 antibody titer >250 U/mL). The EIR rate after the primary vaccination series was 47% and 25% in MM and WM patients, respectively. Following the first and second booster vaccinations, the EIR rates increased to 84% and 91% in MM patients, respectively, and 60% and 89% in WM patients, respectively. Factors associated with lower EIR in MM patients were hypogammaglobulinemia, lymphopenia, and treatment with anti-CD38 monoclonal antibody or corticosteroid. Treatment with a BTK inhibitor or rituximab was associated with a lower EIR in WM patients, while asymptomatic and treatment naïve WM patients had a higher EIR. Functional profiling identified reduced antibody-dependent cellular phagocytosis (ADCP), neutrophil phagocytosis (ADNP), and NK cell activity (ADNKA) against wild-type and variant SARS-CoV-2 (a, b, and g) in both MM and WM patients compared to healthy donors. Our data demonstrate that although MM and WM patients have impaired humoral responses to the primary SARS-CoV-2 vaccination series, repeated booster vaccines significantly improve immunogenicity. The study was registered at ClinicalTrials.gov (#NCT04830046).

Conflict of interest: COI declared - see note

COI notes: ARB received honoraria/research funds from Adaptive, BeiGene, CSL Behring, Genzyme, Karyopharm, Pharmacyclics, and Sanofi. JJC received honoraria from Abbvie, AstraZeneca, Beigene, Cellectar, J&J, Kite, Loxo, and Pharmacyclics, and research funds from Abbvie, AstraZeneca, Beigene, Cellectar, Loxo, and Pharmacyclics. SPT received honoraria/research funds from ADC Therapeutics, AstraZeneca, and Beigene. SRS received honoraria/research funds from ADC Therapeutics, AstraZeneca, and Beigene. PGR received honoraria/research funds from Celgene/BMS, GSK, Jazz Pharma, Karyopharm, Oncopeptides, Regeneron, and Sanofi. AJY: consulting for AbbVie, Adaptive Biotechnologies, Amgen, BMS, Celgene, GSK, Johnson & Johnson, Karyopharm, Oncopeptides, Pfizer, Prothena, Regeneron, Sanofi, Sebia, Takeda; research funding to institution from Amgen, BMS, GSK, Johnson & Johnson, Sanofi. ML received honoraria from Genmab, Sanofi, MJH Life Sciences, Genentech, Center for Business Models, and C4XD.

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Prospective study of immunogenicity to SARS-CoV-2 booster vaccines in multiple myeloma and Waldenström macroglobulinemia

Andrew R. Branagan,[1] Clifton Mo,[2] Matthew Lei,[1] Joshua N. Gustine,[1] Andrew J. Yee,[1] Elizabeth O'Donnell,[1] Jorge J. Castillo,[2] Omar Nadeem,[2] Catherine Flynn,[2] Zachary Bernstein,[1] Rie Nakamoto-Matsubara,[1] Kirsten Meid,[2] Rakesh Verma,[1] Zachary R. Hunter,[2] Maria L. Guerrera,[2] Galit Alter,[3] Jill Burke,[1] Cynthia Harrington,[1] Emerentia Agyemang,[1] Marilyn Gammon,[1] Kathleen Lively,[1] Lisette Packer,[1] Nora Horick,[1] Jacob Laubach,[2] Constantine Mitsiades,[2] Nikhil Munshi,[2] Kenneth C. Anderson,[2] Steven P. Treon,[2] Paul G. Richardson,[2] Noopur S. Raje,[1] and Shayna R. Sarosiek.[2]

[1]Massachusetts General Hospital Cancer Center, Boston MA; [2]Dana-Farber Cancer Institute, Boston, MA; [3]Ragon Institute of Mass General, MIT, and Harvard, Cambridge, MA.

Corresponding Author:
Andrew Branagan, MD, PhD
Center for Multiple Myeloma
Massachusetts General Hospital
55 Fruit Street, Boston, MA, 02114 USA
Tel: 617-724-4000
Email: abranagan@mgh.harvard.edu

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KEY POINTS

We show for the first time that 2 SARS-CoV-2 booster vaccinations can overcome ineffective responses in nearly 90% of MM and WM patients.

Despite eliciting SARS-CoV-2 antibodies, we show that MM and WM patients have decreased antibody-mediated effector functions.

ABSTRACT

Patients with multiple myeloma (MM) and Waldenström macroglobulinemia (WM) have increased risk of severe COVID-19. Impaired humoral responses to the primary vaccination series against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been reported in MM and WM patients, but impact of booster vaccinations and functional status of the elicited antibodies is unknown. We performed a prospective cohort study investigating SARS-CoV-2 vaccination in MM (n=93) and WM (n=48) patients. The primary endpoint was effective immune response (EIR) at 28 days after the primary vaccination series (i.e., anti-spike SARS-CoV-2 antibody titer >250 U/mL). The EIR rate after the primary vaccination series was 47% and 25% in MM and WM patients, respectively. Following the first and second booster vaccinations, the EIR rates increased to 84% and 91% in MM patients, respectively, and 60% and 89% in WM patients, respectively. Factors associated with lower EIR in MM patients were hypogammaglobulinemia, lymphopenia, and treatment with anti-CD38 monoclonal antibody or corticosteroid. Treatment with a BTK inhibitor or rituximab was associated with a lower EIR in WM patients, while asymptomatic and treatment naïve WM patients had a higher EIR. Functional profiling identified reduced antibody-dependent cellular phagocytosis (ADCP), neutrophil phagocytosis (ADNP), and NK cell activity (ADNKA) against wild-type and variant SARS-CoV-2 (α, β, and γ) in both MM and WM patients compared to healthy donors. Our data demonstrate that although MM and WM patients have impaired humoral responses to the primary SARS-CoV-2 vaccination series, repeated booster vaccines significantly improve immunogenicity. The study was registered at ClinicalTrials.gov (#NCT04830046).

INTRODUCTION

Plasma cell dyscrasias (PCD), such as multiple myeloma (MM) and Waldenström macroglobulinemia (WM), are hematologic malignancies characterized by the proliferation of neoplastic plasma cells in the bone marrow (BM) that secrete a monoclonal immunoglobulin. The rate of infections is higher in patients with a PCD compared to the general population,[1,2] and infection is a leading cause of morbidity and mortality.[3,4] The increased susceptibility to infection is due to the immunosuppression caused by the disease itself, as well as the treatment regimens and host-related factors (e.g., age, comorbidities, frailty).[5]

Impaired humoral immunity due to B-cell dysfunction frequently occurs with PCD and manifests as hypogammaglobulinemia (i.e., suppression of uninvolved polyclonal immunoglobulins).[5,6] Defects in cellular and innate immunity have also been described, including T-cells, natural killer (NK) and dendritic cells, alternative complement pathway, and neutropenia.[5,7-12] This immune dysfunction is often exacerbated by the treatments used for PCD. Specifically, therapies that deplete the B-cell and plasma cell compartments by targeting B-cell maturation antigen (BCMA), CD38, CD20, and Bruton's tyrosine kinase (BTK) may worsen hypogammaglobulinemia.[5,13-15] T-cell immunodeficiency can be caused by proteasome inhibitors, anti-CD38 monoclonal antibodies, and the lymphodepleting chemotherapy administered for chimeric antigen receptor T-cell (CAR-T) therapy.[5,16-19] Corticosteroids and autologous stem cell transplantation (ASCT) are also highly immunosuppressive.[20]

The mechanisms underlying the immunosuppression in PCD also result in impaired immune responses to vaccinations. Although there is limited data in WM patients,[21] suboptimal antibody production has been reported in MM patients following vaccination against *Streptococcus pneumoniae* and seasonal influenza.[22,23] For example, one study showed that the standard influenza vaccination resulted in seroprotection in only <20% of MM patients.[22] However, using either a two-dose or three-dose series of a high-dose influenza vaccination significantly improves the immunogenicity in MM patients,[24,25]

highlighting the need to develop vaccination strategies for this specific patient population.

Patients with a PCD have an increased risk of severe complications with the coronavirus disease 2019 (COVID-19) caused by severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV-2).[26] Impaired antibody-mediated responses to the primary vaccination series for SARS-CoV-2 have been reported in both MM and WM patients,[27-34] but there is limited data on the impact of booster vaccinations on immunogenicity.

We performed a prospective cohort study to compare the vaccine responses against SARS-CoV-2 in patients with MM and WM. We assessed responses to both the primary and booster vaccinations and identified clinical factors predictive of a vaccine response.

METHODS

Patients and study design

This prospective cohort study was approved by the Dana-Farber/Harvard Cancer Center Institutional Review Board and complied with the Declaration of Helsinki and Good Clinical Practice Guidelines. Patients were enrolled at the Massachusetts General Hospital Cancer Center and Dana-Farber Cancer Institute. All patients provided written consent. The study was registered at ClinicalTrials.gov (#NCT04830046).

Inclusion criteria were age ≥18 years and a diagnosis of MM or WM per the International Myeloma Working Group (IMWG) and World Health Organization (WHO) criteria, respectively. Eligible patients had intended to receive a SARS-CoV-2 vaccination within 60 days, and none had received a prior SARS-CoV-2 vaccination. We excluded patients with a prior COVID-19 infection by clinical history and/or serological testing (i.e., positive baseline SARS-CoV-2 antibody titer). The two-cohort trial design is shown in **Figure 1**. MM patients were assigned to Cohort 1, and WM patients were

assigned to Cohort 2. WM patients in Cohort 2 were assigned into three subgroups based on treatment history: Cohort 2A (treatment naïve), Cohort 2B (active treatment with BTK inhibitor [BTKi]), and Cohort 2C (previously or currently treated, excluding BTKi).

The primary study endpoint was the effective immune response (EIR) rate at 28 days following the second or final dose of the primary vaccination series against SARS-CoV-2. EIR was defined as a positive anti-spike SARS-CoV-2 antibody titer >250 U/mL.[29] Key secondary endpoints were to investigate the following: (1) durability of an EIR following vaccination; (2) clinical correlates of attaining an EIR; (3) rates of COVID-19 infection following vaccination; and (4) functional biomarkers of immune response.

Study assessments

Patient and disease characteristics, treatment history, complete blood counts, and immunoglobulin levels were obtained at baseline. SARS-CoV-2 serologies were assessed at baseline and after the primary vaccination series at 28 days and 12 months. Serologies were also obtained after booster vaccinations in a subset of patients. SARS-CoV-2 serologies were measured with a quantitative electrochemiluminescence immunoassay that detects antibodies to the SARS-CoV-2 spike protein receptor binding domain (Roche Diagnostics). SARS-CoV-2 antibody titer ≥0.80 U/mL was considered positive.

Vaccine administration

SARS-CoV-2 vaccines were obtained through commercial supply and were administered per the package insert. Specific vaccine product selection was based on the availability of BNT162b2 (Pfizer-BioNTech), mRNA-1273 (Moderna), or JNJ-78436735 (Johnson & Johnson). The primary vaccination series for BNT162b2 and mRNA-1273 included two doses of the original monovalent vaccine, while JNJ-78436735 included one dose of the monovalent vaccine.

Functional antibody profiling

Functional profiling occurred in 3 cohorts: MM patients (n=23), WM patients (n=14), and non-cancer (NC) healthy donors (n=14). Plasma was collected in all patients after receiving two doses of an mRNA SARS-CoV-2 vaccine (i.e., primary vaccination series). As previously described, spike antibody subclasses and isotypes against SARS-CoV-2 wild-type (WT) and variants of concern were quantified.[35] Antibody-dependent cellular phagocytosis (ADCP), antibody-dependent neutrophil phagocytosis (ADNP), antibody-dependent complement depositions (ADCD), and antibody-dependent NK cell activity (ADNKA) were also performed as before.[35]

Statistical analyses

Baseline clinical characteristics were summarized using descriptive statistics with median/range for continuous variables and numbers/percentages for categorical variables. Non-parametric comparisons of continuous variables were made using the Mann-Whitney U test or Kruskal-Wallis test. Comparisons of categorical variables were made using the Fisher's exact test or Chi-square test. Logistic regression models were fitted to identify predictors of attaining an EIR following the SAR-CoV-2 vaccination; results are presented as odds ratio (OR) with 95% confidence interval (CI). P-values <0.05 were considered statistically significant. All analyses were performed in the R software (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient characteristics

Between June 2019 and August 2021, 150 patients were enrolled, of whom 9 were excluded from the final analysis due to baseline serologic evidence of prior COVID-19 infection (n=6) or did not receive vaccination (n=3) (**Figure 1**). The final cohort included

141 patients: 93 MM patients (Cohort 1) and 48 WM patients (Cohort 2). Among the WM patients, there were 10, 21, and 17 patients in Cohorts 2A, 2B, and 2C, respectively. The baseline clinical characteristics for the MM and WM patients are shown in **Tables 1 and 2**, respectively. All patients included in the final cohort received a primary SARS-CoV-2 vaccination series: BNT162b2 (n=77; 55%), mRNA-1273 (n=51; 36%), and JNJ78436735 (n=13; 9%).

Humoral response to SARS-CoV-2 vaccination

Overall, the EIR rate at 28 days following the primary SARS-CoV-2 vaccination series (i.e., anti-spike antibody >250 U/mL) was 47% in MM patients and 25% in WM patients (**Table 3**). A positive titer (i.e., anti-spike antibody ≥0.8 U/mL) was observed in 94% of MM patients and 65% of WM patients, and the median anti-spike antibody titer was 188.0 U/mL (range, 0-4161 U/mL) and 2.2 U/mL (range, 0-2500 U/mL), respectively. Among WM patients, the EIR rates in treatment naïve (Cohort 2A), active BTKi therapy (Cohort 2B), and previously/currently treated (Cohort 2C) subgroups were 60%, 10%, and 24%, respectively.

At least one booster vaccination against SARS-CoV-2 was administered in 79 MM patients (1 booster: n=27; 2 boosters: n=52) and 45 WM patients (1 booster: n=20; 2 boosters: n=25). The median time from completing the primary vaccination series to first and second booster in MM patients was 5.1 and 11.3 months, respectively, and in WM patients was 4.3 and 10.0 months, respectively. The EIR rates following the first and second booster vaccinations were 84% and 91% in MM patients, respectively, and 60% and 89% in WM patients, respectively. At 12 months following the primary SARS-CoV-2 vaccination series (including the subsequent booster vaccinations), the EIR rate was 85% and 83% in MM and WM patients, respectively. All tested patients had a positive anti-spike antibody titer at 12 months.

Predictors of humoral response to SARS-CoV-2 vaccination

We performed a pre-planned univariate analysis to identify baseline clinical factors associated with a humoral response to SARS-CoV-2 vaccination (i.e., EIR at 28 days following primary vaccination series) (**Table 4**). In MM patients, the EIR rate was significantly lower with hypogammaglobulinemia (6% vs 57%; p<0.001), lymphopenia (32% vs 68%; p<0.001), and active treatment with an anti-CD38 monoclonal antibody (31% vs 56%; p=0.03) or corticosteroid (30% vs 60%; p=0.006). Current (<2 months) anti-CD38 monoclonal use was also associated with a significantly lower EIR rate (31% vs 63%; p=0.004). MM patients with an IgG isotype had a significantly higher EIR rate (59% vs 33%; p=0.02). In WM patients, the EIR rate was significantly lower if on active treatment with a BTKi (10% vs 50%; p=0.01) or rituximab (0% vs 50%; p=0.04), whereas asymptomatic (63% vs 18%; p=0.01) and treatment naïve patients (50% vs 17%; p=0.04) had a significantly higher EIR rate. Compared to BNT162b2, a primary vaccination series with mRNA-1273 was associated with a significantly higher EIR rate in both MM (65% vs 39%; p=0.03) and WM (53% vs 11%; p=0.004) patients.

Functional characterization of humoral response to SARS-CoV-2 vaccination

We performed a functional characterization of the WT SARS-CoV-2 spike antibodies that were generated following a primary mRNA-based vaccination series in patients with MM (n=23), WM (n=14), and NC healthy donors (n=14). WT SARS-CoV-2 spike antibodies (i.e., IgG_1, IgG_3, IgM, and IgA) were detected in all tested patients. MM and WM patients had similar WT spike antibody titers compared to NC, with the exception of a lower IgG_1 in WM patients (**Figure 1A-D)**. FcγR2A, FcγR2B, and FcγR3A titers for WT SARS-CoV-2 were also similar (**Figure 1E-G)**. Spike-specific ADCP, ADNP, and ADNKA responses to WT SARS-CoV-2 were significantly lower in MM and WM patients, while ADCD responses were preserved (**Figure 1H-L)**.

Spike antibodies for SARS-CoV-2 variants of concern were also evaluated, including the α (B.1.1.7), β (B.1.351), and γ (P.1) variants (**Figure 2**). For all three variants, the IgG_1 titer and ADNP and ADCP responses were significantly lower in MM and WM patients compared to NC.

Breakthrough COVID-19 infections

Nineteen patients (13%) developed a COVID-19 infection within 12 months after the initial SARS-CoV-2 vaccination. The incidence of a breakthrough COVID-19 infection in MM and WM patients was 17% (n=16/93) and 6% (n=3/48), respectively. Among those with a breakthrough infection, 9 patients (47%) had attained an EIR (all MM patients). Severe COVID-19 infection requiring hospitalization occurred in 6 patients, of whom all had MM. There were no deaths related to COVID-19 and treatment consisted of anti-viral therapy, corticosteroids, protocol-directed treatment, and best supportive care.

DISCUSSION

We performed a prospective study to investigate the humoral responses to SARS-CoV-2 vaccination in MM and WM patients. Our findings show that the majority of patients exhibited low antibody responses to the primary SARS-CoV-2 vaccination series. Only 47% of MM patients and 25% of WM patients achieved an EIR to the primary vaccination series. These results add to the collective evidence of low vaccine responses against SARS-CoV-2, seasonal influenza, and *Streptococcus pneumoniae* in MM and WM patients,[22,23,27,28,30-34] and highlights that humoral immune dysfunction is a hallmark of both these hematologic malignancies.

An important finding was the benefit of booster vaccinations on improving EIR rates against SARS-CoV-2. Despite low responses to the primary SARS-CoV-2 vaccination series, we show for the first time that two booster vaccinations can lead to an EIR in nearly 90% of MM and WM patients. This response rate compares favorably to that described with only one booster vaccination,[36] and indicates that repeated antigen exposure through booster vaccinations may overcome the impaired humoral response intrinsic to MM and WM. A dose-response relationship with immunogenicity has also been reported with the influenza vaccine in MM patients.[24] Compared to a single standard vaccine (20%), the use of a two-dose series with a high-dose influenza

vaccine resulted in antibody production in 47% and 65% of patients after one and two doses, respectively.[24] Preliminary results from a recent randomized trial also showed that using a three-dose series of high-dose influenza vaccine at 0, 2, and 4 months significantly improved immunogenicity compared to one high-dose vaccination.[25] Collectively, these results may also explain our observation of higher vaccine responses with mRNA-1273 compared to BNT162b2. Although both vaccines encode nearly the same product, the mRNA-1273 formulation utilized during the study period contained a higher mRNA dose than BNT162b2 (100 μg vs 30 μg),[37,38] suggesting that the higher antigen exposure with mRNA-1273 accounts for the differences in response rates.[29,34]

Our study provides the framework to herald the development of novel vaccination strategies in MM and WM patients. The dose-response relationship between SARS-CoV-2 booster vaccinations and antibody production demonstrates that repeated antigen exposure is a strategy to improve immunogenicity in MM and WM patients. Using a high-dose vaccine is an alternative strategy, as first described with the seasonal influenza vaccine in MM patients.[24] These strategies should be prospectively evaluated in MM and WM patients for other vaccine-preventable pathogens, such as *Streptococcus pneumoniae*, respiratory syncytial virus, and herpes zoster. In particular, there is an urgent need to improve protection against invasive pneumococcal disease in MM patients, who have a 154-fold increased risk of infection compared to the general population and a case fatality rate of 18%.[39] There are currently four commercially available vaccines against *Streptococcus pneumoniae* (i.e., PCV13, PCV20, PCV21, PPSV23), and novel pneumococcal vaccine schedules that increase antigen exposure should be investigated in MM patients.

In contrast to prior studies, we investigated the effector functions of anti-spike antibodies produced following SARS-CoV-2 vaccination. Despite the production of SARS-CoV-2 antibodies, we show that MM and WM patients have decreased antibody-mediated effector functions (e.g., cellular and neutrophil phagocytosis, NK cell cytotoxicity). The discovery of impaired opsonophagocytic function indicates that the humoral immune dysfunction in MM and WM patients extends beyond just

hypogammaglobulinemia. Moreover, it may provide a mechanistic insight to explain the breakthrough COVID-19 infections we and others have observed despite antibody production following vaccination.[40] While we did not investigate the role of T-cell responses to SARS-CoV-2 vaccination in this study, previous reports indicate such impairments exist in MM and WM patients and likely contribute to breakthrough infections.[32,41,42] Taken together, these findings highlight the need for ongoing strategies beyond vaccination in managing COVID-19 in MM and WM patients. This includes the use of intravenous immunoglobulin, monoclonal antibodies (e.g., pemivibart), and anti-viral agents (e.g., remdesivir, nirmatrelvir-ritonavir), especially since immunocompromised patients remain at high risk for severe COVID-19 even in the post-pandemic era.[43]

Specific anti-neoplastic therapies adversely impacted responses to SARS-CoV-2 vaccination. Akin to previous studies,[30-32,34,44,45] agents that deplete the B-cell and plasma cell compartment and cause hypogammaglobulinemia—such as daratumumab, isatuximab, rituximab, and BTKi—were associated with lower vaccine responses. Additionally, corticosteroids were linked to reduced responses to SARS-CoV-2 vaccination. We could not assess the impact of BCMA-directed therapies (e.g., bispecific antibodies, CAR-T) given too few patients as the study was initiated early in the COVID-19 pandemic, just prior to approval of any BCMA-directed therapies. However, we anticipate similarly low vaccine responses given the B-cell aplasia and hypogammaglobulinemia associated with these treatments.[19] Timing the administration of the SARS-CoV-2 vaccination around these offending anti-neoplastic agents whenever possible may be a strategy to enhance immunogenicity. The IMWG infection guidelines recommend this strategy for other vaccinations and should be extended to MM and WM patients receiving the SARS-CoV-2 vaccination.[5] In WM patients, temporary interruption of BTKi peri-vaccination was evaluated as a potential strategy to improve immunogenicity, but the increased antibody production was only transient.[46] Caution is needed with this approach since temporary interruption of BTKi is associated with a withdrawal syndrome and shorter progression-free survival in WM patients.[47,48] By contrast, in MM patients, holding monoclonal antibody therapy around vaccination is

both reasonable and feasible, and in the context of combination therapy is unlikely to result in disease progression in the majority of patients.[49,50]

This multicenter study has several important strengths, including a prospective design, high rates of booster vaccination, and functional studies examining the anti-spike antibodies produced after SARS-CoV-2 vaccination. A limitation is the lack of comparator group of healthy individuals, though earlier studies established an impaired humoral response to SARS-CoV-2 vaccination in MM and WM patients.[27,28,30-33] This study was also not designed to assess vaccine effectiveness against COVID-19 infection, and antibody levels are used are surrogates. We defined an adequate immune response (i.e., EIR) as an anti-spike antibody titer greater than 250 U/mL, akin to a prior study evaluation the SARS-CoV-2 vaccination in MM patients.[29] However, there is no clear antibody titer to define protection against SARS-CoV-2 in MM and WM patients. This is further emphasized by our data showing antibody-mediated effector cell dysfunction can occur despite antibody production. Notably, this study was not designed to compare vaccine responses between MM and WM patients, and any direct comparison would be confounded by differences in treatment regimens and comorbidities. Lastly, the rate of infection overall and hospitalization for severe disease without any mortality is encouraging and collectively reflects the progress in vaccination, treatment, and supportive care during the pandemic.[51,52]

In summary, this prospective study demonstrates that MM and WM patients have impaired humoral responses to SARS-CoV-2 vaccination, including both antibody production and antibody-mediated effector cell function. Anti-neoplastic therapies that deplete the B-cell and plasma cell compartments adversely impacted vaccine responses, but two booster vaccinations against SARS-CoV-2 significantly improved immunogenicity. Our study provides a framework for the development of vaccination strategies specific for MM and WM patients.

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AUTHOR CONTRIBUTIONS

ARB conceived the idea; ML, ZB, RNM, MG, MLG, KL, LP, and RV collected data; JNG, ML, GA, and NH analyzed the data; SRS, CM, AY, NR, EA, JB, CH, NO, JJC, CF, PGR, and EO enrolled subjects on the study; ARB and JNG wrote the initial manuscript draft; and all authors aided in interpreting the data and critically reviewed and edited the manuscript.

DISCLOSURES

ARB received honoraria/research funds from Adaptive, BeiGene, CSL Behring, Genzyme, Karyopharm, Pharmacyclics, and Sanofi. JJC received honoraria from Abbvie, AstraZeneca, Beigene, Cellectar, J&J, Kite, Loxo, and Pharmacyclics, and research funds from Abbvie, AstraZeneca, Beigene, Cellectar, Loxo, and Pharmacyclics. SPT received honoraria/research funds from ADC Therapeutics, AstraZeneca, and Beigene. SRS received honoraria/research funds from ADC Therapeutics, AstraZeneca, and Beigene. PGR received honoraria/research funds from Celgene/BMS, GSK, Jazz Pharma, Karyopharm, Oncopeptides, Regeneron, and Sanofi. AJY: consulting for AbbVie, Adaptive Biotechnologies, Amgen, BMS, Celgene, GSK, Johnson & Johnson, Karyopharm, Oncopeptides, Pfizer, Prothena, Regeneron, Sanofi, Sebia, Takeda; research funding to institution from Amgen, BMS, GSK, Johnson & Johnson, Sanofi. ML received honoraria from Genmab, Sanofi, MJH Life Sciences, Genentech, Center for Business Models, and C4XD.

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Table 1. Baseline clinical characteristics of patients with multiple myeloma prior to the initial SARS-CoV-2 vaccination (Cohort 1).

Patient Characteristic	**All Patients (N=93)**
Age	
Median (range)	65 (44-84)
>75 years – no. (%)	7 (8)
Male sex – no. (%)	48 (52)
Race – no. (%)	
White	83 (89)
Non-white	10 (11)
COVID-19 vaccine – no. (%)	
BNT162b2	49 (53)
mRNA-1273	34 (37)
JNJ-78436735	10 (11)
R-ISS stage – no. (%)	
I	46/85 (54)
II	24/85 (28)
III	15/85 (18)
Involved heavy and/or light chain – no. (%)	
IgG	51 (55%)
IgA	16 (17%)
Kappa	61 (66%)
Lambda	24 (26%)
Non-secretory	1 (1%)
Median monoclonal protein – g/dL (range)	0.05 (0-3.68)
Treatment status – no. (%)	
Treatment naïve	8 (9)
Previously treated	85 (91)
Median no. prior treatment lines (range)	1 (1-7)
Current treatment regimens* – no. (%)	
Immunomodulatory agent	46 (53)
Corticosteroid	40 (46)
Proteasome inhibitor	35 (40)
Anti-CD38 monoclonal Ab	32 (37)
BCMA CAR-T	12 (14)
Alkylating agent	4 (5)
Belantamab mafodotin	1 (1)
Elotuzumab	1 (1)
Hypogammaglobulinemia (IgG <400 mg/dL) – no. (%)	17 (18)
IVIG within 90 days – no. (%)	13 (14)
Co-morbidities – no. (%)	
Pulmonary disease	10 (11)
Chronic kidney disease	2 (2)
Diabetes	12 (13)
Hypertension	53 (57)

Cardiovascular disease	6 (6)
Obesity (BMI >30 kg/m^2)	39 (42)
Current tobacco use	0 (0)

*Among patients who were receiving active treatment at the time of vaccination (n=87).

Table 2. Baseline clinical characteristics of patients with Waldenström macroglobulinemia prior to the initial SARS-CoV-2 vaccination (Cohort 2).

Patient Characteristic	**All Patients (N=48)**
Age	
Median (range)	67 (49-81)
>75 years – no. (%)	5 (10)
Male sex – no. (%)	28 (58)
Race – no. (%)	
White	46 (96)
Non-white	2 (4)
COVID-19 vaccine – no. (%)	
BNT162b2	28 (58)
mRNA-1273	17 (35)
JNJ-78436735	3 (6)
MYD88 mutation – no. (%)	
Mutated	35 (73)
Wild type	8 (17)
Unknown	5 (10)
CXCR4 mutation – no. (%)	
Mutated	11 (23)
Wild type	12 (25)
Unknown	25 (52)
Asymptomatic WM – no. (%)	8 (17)
Treatment status – no. (%)	
Treatment naïve	12 (25)
Previously treated	36 (75)
Median no. prior treatment lines (range)	1 (1-4)
Current treatment regimens* – no. (%)	
BTK inhibitor	21 (58)
Rituximab	8 (17)
Venetoclax	4 (8)
Bendamustine	2 (4)
Proteasome inhibitor	2 (4)
Corticosteroid	2 (4)
Fludarabine	1 (2)
Median serum immunoglobulin level – mg/dL (IQR)	
IgM	837 (39-5835)
IgG	598 (121-1825)
IgA	42 (5-285)
Hypogammaglobulinemia (IgG <400 mg/dL) – no. (%)	34 (71)
IVIG within 90 days – no. (%)	5 (10)
Co-morbidities – no. (%)	
Pulmonary disease	7 (15)
Chronic kidney disease	6 (13)
Diabetes	1 (2)

Hypertension	15 (31)
Cardiovascular disease	7 (15)
Obesity (BMI >30 kg/m^2)	5 (10)
Current tobacco use	6 (13)

*Among patients who were receiving active treatment at the time of vaccination (n=36).

Table 3. Humoral responses to SARS-CoV-2 vaccination in multiple myeloma and Waldenström macroglobulinemia.

Vaccine Responses	Cohort 1: MM (N=93)	Cohort 2: WM			
		All Patients (n=48)	2A (N=10)	2B (N=21)	2C (N=17)
28 days after primary vaccination series					
EIR – no. (%)	44/93 (47%)	12/48 (25%)	6/10 (60%)	2/21 (10%)	4/17 (24%)
Positive Ab titer – no. (%)	87/93 (94%)	31/48 (65%)	9/10 (90%)	12/21 (57%)	10/17 (59%)
Median Ab titer – U/mL (range)	188.0 (0-4161)	2.2 (0-2500)	282.3 (0-2500)	0.8 (0-2500)	0.6 (0-2500)
After 1st booster					
EIR – no. (%)	66/79 (84%)	25/42 (60%)	7/10 (70%)	12/19 (63%)	6/13 (46%)
Positive Ab titer – no. (%)	79/79 (100%)	31/42 (74%)	9/10 (90%)	14/19 (74%)	8/13 (62%)
Median Ab titer – U/mL (range)	5130 (3.2-25,000)	998.5 (0-25,000)	2500 (0-25,000)	1215 (0-12,500)	9.1 (0-2500)
After 2nd booster					
EIR – no. (%)	30/33 (91%)	16/18 (89%)	4/4 (100%)	6/7 (86%)	6/7 (86%)
Positive Ab titer – no. (%)	33/33 (100%)	17/18 (94%)	5/5 (100%)	6/7 (86%)	7/7 (100%)
Median Ab titer – U/mL (range)	8169 (52.2-25,000)	3379 (0-12,500)	5829 (2996-12,500)	2506 (0-7996)	5731 (58.3-12,500)
12 months after primary vaccination series +/- booster(s)					
EIR – no. (%)	68/80 (85%)	33/40 (83%)	8/10 (80%)	14/17 (82%)	11/13 (85%)
Positive Ab titer – no. (%)	80/80 (100%)	40/40 (100%)	10/10 (100%)	17/17 (100%)	13/13 (100%)
Median Ab titer – U/mL (range)	3955 (3.6-25,000)	2063 (0.4-25,000)	3086 (11.2-25,000)	1843 (0.4-10,908)	3414 (0.8-12,500)

MM, multiple myeloma; WM, Waldenström macroglobulinemia; EIR, effective immune response; Ab, antibody.

Table 4. Predictors of an effective immune response at 28 days after primary SARS-CoV-2 vaccination series in multiple myeloma and Waldenström macroglobulinemia.

	OR (95% CI)	P-value
Multiple myeloma		
Age >75 years	0.17 (0.01-1.49)	0.11
Male sex	1.34 (0.55-3.29)	0.54
Non-white race	1.77 (0.39-9.16)	0.51
mRNA-1273 (vs BNT162b2)	**2.86 (1.07-7.97)**	**0.03**
R-ISS stage III (vs I/II)	0.53 (0.13-1.93)	0.39
IgG isotype (vs non-IgG)	**2.82 (1.13-7.32)**	**0.02**
Treatment naïve	1.12 (0.20-6.45)	1.00
Current treatment		
IMiD	1.74 (0.71-4.33)	0.22
PI	0.43 (0.16-1.10)	0.06
Anti-CD38 mAb	**0.37 (0.13-0.97)**	**0.03**
BCMA CAR-T	1.11 (0.01-89.4)	1.00
Corticosteroid	**0.29 (0.11-0.73)**	**0.006**
Previous ASCT	1.59 (0.60-4.27)	0.37
CR (vs <CR)	1.27 (0.42-3.89)	0.80
>1 prior treatment line (vs 0-1)	0.35 (0.10-1.05)	0.07
Hypogammaglobulinemia	**0.04 (0.01-0.25)**	**0.004**
IVIG within 90 days	0.29 (0.05-1.24)	0.08
ALC <1000/μL	**0.23 (0.09-0.54)**	**<0.001**
Pulmonary disease	1.13 (0.24-5.30)	1.00
Chronic kidney disease	1.11 (0.01-89.4)	1.00
Diabetes	1.66 (0.41-7.20)	0.54
Hypertension	0.58 (0.23-1.44)	0.22
Cardiovascular disease	1.12 (0.14-8.84)	1.00
Obesity	1.87 (0.75-4.71)	0.15
Current tobacco use	UTC	UTC
Waldenström macroglobulinemia		
Age>65 years	2.93 (0.60-19.6)	0.18
Male sex	0.38 (0.06-1.86)	0.31
Non-white race	UTC	UTC
mRNA-1273 (vs BNT162b2)	**8.82 (1.69-63.4)**	**0.004**
MYD88 mutation	0.63 (0.08-7.83)	0.63
CXCR4 mutation	0.32 (0.01-4.77)	0.59
Asymptomatic WM	**7.86 (1.58-46.5)**	**0.01**
Treatment naïve	**4.80 (1.03-26.2)**	**0.04**
Current BTK inhibitor use	**0.11 (0.01-0.85)**	**0.01**
Current rituximab use	**UTC**	**0.04**
Progressive disease	2.90 (0.34-19.8)	0.28
>1 prior treatment line (vs 0-1)	3.29 (0.51-21.7)	0.20
Hypogammaglobulinemia	1.36 (0.27-9.37)	1.00
IVIG within 90 days	2.24 (0.16-23.0)	0.58

ALC <1000/μL	0.87 (0.46-1.13)	0.48
Pulmonary disease	1.23 (0.10-9.13)	1.00
Chronic kidney disease	0.57 (0.01-5.97)	1.00
Diabetes	UTC	UTC
Hypertension	0.67 (0.10-3.40)	0.73
Cardiovascular disease	1.23 (0.10-9.13)	1.00
Obesity	0.73 (0.01-8.52)	1.00
Current tobacco use	0.57 (0.01-5.97)	1.00

R-ISS, Revised Multiple Myeloma International Staging System; IMiD, immunomodulatory agent; PI, proteasome inhibitor; mAb, monoclonal antibody; IVIG, intravenous immunoglobulin; BTK, Bruton's tyrosine kinase; ALC, absolute lymphocyte count; OR, odds ratio; CI, confidence interval; UTC, unable to calculate.

FIGURE LEGENDS

Figure 1. CONSORT diagram.

Figure 2. Functional profiling of SARS-CoV-2 wild-type spike antibody responses.
A-G.) Box plots of IgG1, IgG3, IgM, IgA, FcR2A, FcR2B, FcR3A, or FcR3B titers in log10 median fluorescence intensity (MFI). Lines represent the minimum, lower quartile, median, upper quartile, and maximum. Statistical significance between groups were tested with a non-parametric Kruskal-Wallis multiple comparisons test. P-values are as indicated.

H.) Truncated violin plot of phagoscores from Antibody-Dependent THP-1-mediated Cellular Phagocytosis assay (ADCP). The dashed lines represent quartiles, with a solid black line for median. Statistical significance between groups were tested with a non-parametric Kruskal-Wallis multiple comparisons test. P-values are indicated as follows: 0.1234 (ns), 0.0332 (*), 0.0021 (**), 0.0002 (***), and <0.0001 (****).

I.) Truncated violin plot of phagoscores from Antibody-Dependent Neutrophil Phagocytosis (ADNP) assay. The dashed lines represent quartiles, with a solid black line for median. Statistical significance between groups were tested with a non-parametric Kruskal-Wallis multiple comparisons test. P-values are indicated as follows: 0.1234 (ns), 0.0332 (*), 0.0021 (**), 0.0002 (***), and <0.0001 (****).

J.) Box plot of Antibody-Dependent complement Deposition (ADCD) shown as the MFI of FITC-positive beads. Lines represent the minimum, lower quartile, median, upper quartile, and maximum. Statistical significance between groups were tested with a non-parametric Kruskal-Wallis multiple comparisons test. P-values are as indicated.

K-L.) Truncated violin plots of Antibody-Dependent NK cell Activation (ADNKA): percentage of CD107a-positive NK cells or percentage of IFN-g-positive NK cells. The dashed lines represent quartiles, with a solid black line for median. Statistical significance between groups were tested with a non-parametric Kruskal-Wallis multiple comparisons test. P-values are indicated as follows: 0.1234 (ns), 0.0332 (*), 0.0021 (**), 0.0002 (***), and <0.0001 (****).

Figure 3. Functional profiling of SARS-CoV-2 variants of concern spike antibody responses.

A-G.) Box plots of B.1.17 S-, B.1.351 S-, B.1.617 S-specific IgG1, IgG3, IgM, IgA, FcR2A, FcR2B, FcR3A, or FcR3B titers in log10 median fluorescence intensity (MFI). Lines represent the minimum, lower quartile, median, upper quartile, and maximum. Statistical significance between groups were tested with a non-parametric Kruskal-Wallis multiple comparisons test. P-values are as indicated.

H-J.) Truncated violin plots of B.1.17 S-, B.1.351 S-, directed ADNP. The dashed lines represent quartiles, with a solid black line for median. Statistical significance between groups were tested with a non-parametric Kruskal-Wallis multiple comparisons test. P-values are indicated as follows: 0.1234 (ns), 0.0332 (*), 0.0021 (**), 0.0002 (***), and <0.0001 (****).

K-M.) Truncated violin plots of B.1.17 S-, B.1.351 S-, directed ADCP. The dashed lines represent quartiles, with a solid black line for median. Statistical significance between groups were tested with a non-parametric Kruskal-Wallis multiple comparisons test. P-values are indicated as follows: 0.1234 (ns), 0.0332 (*), 0.0021 (**), 0.0002 (***), and <0.0001 (****).

Figure 1.

Figure 1

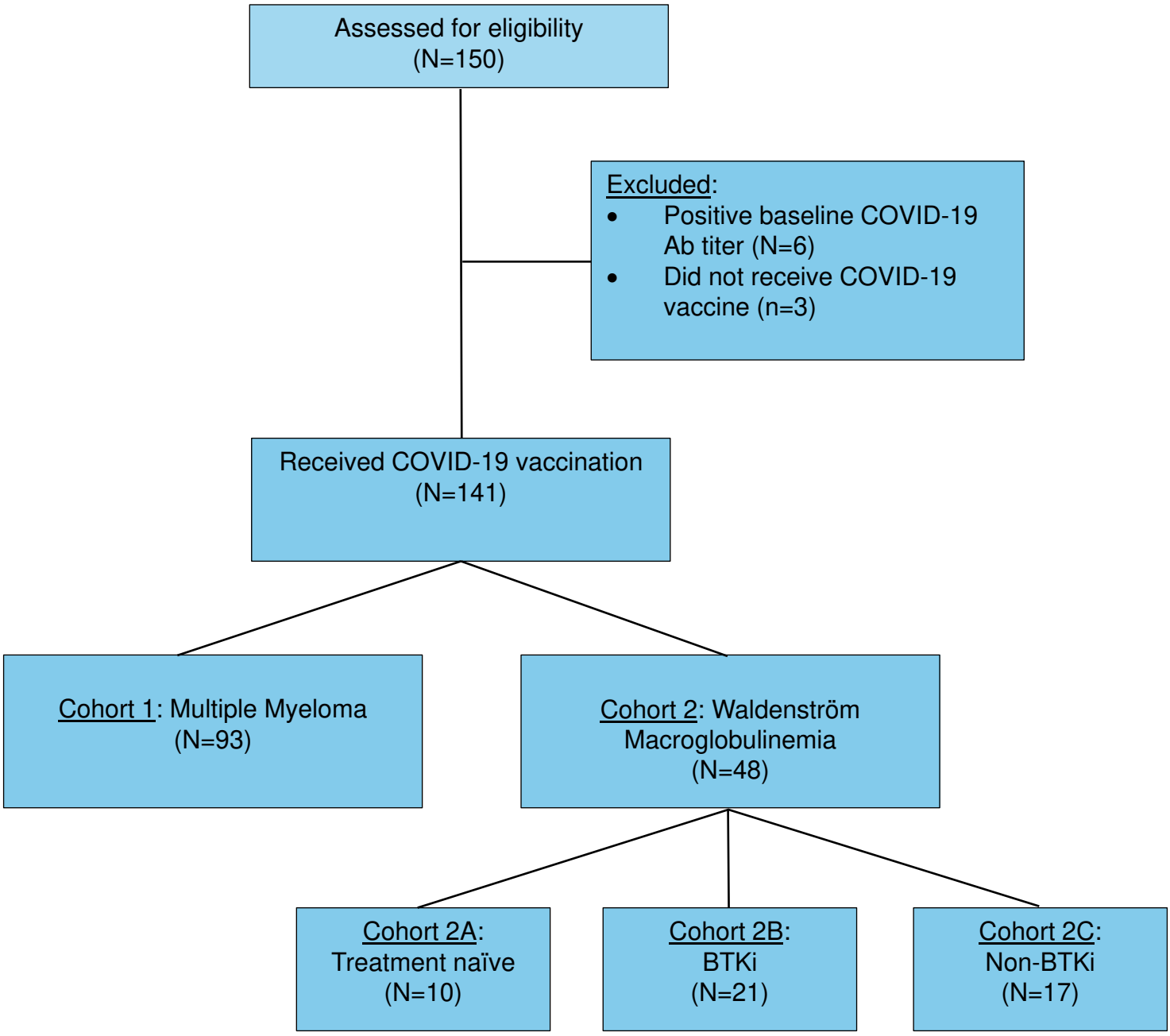

Figure 2.

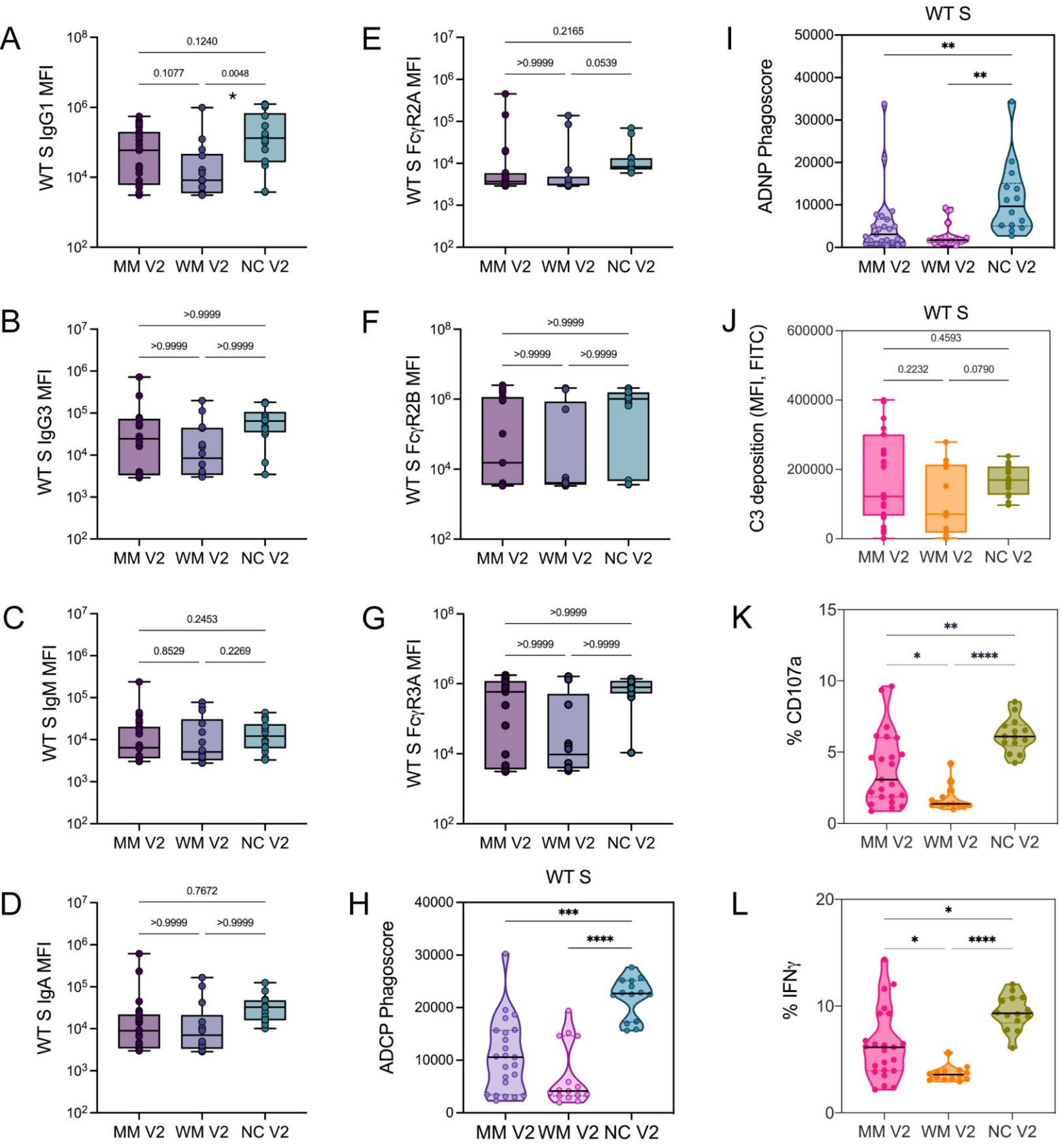

Figure 3.