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Evangelos Terpos (National and Kapodistrian University of Athens, School of Medicine, Greece) Ioannis Trougakos (National and Kapodistrian University of Athens, Greece) Maria Gavriatopoulou (NATIONAL AND KAPODISTRIAN UNIVERSITY OF ATHENS, Greece) Ioannis Papassotiriou (Aghia Sophia Children's Hospital, Greece) Aimilia Sklirou (NATIONAL AND KAPODISTRIAN UNIVERSITY OF ATHEN, Greece) Ioannis Ntanasis-Stathopoulos (National and Kapodistrian University of Athens, Greece, Greece) Eleni-Dimitra Papanagnou (National and Kapodistrian University of Athens (NKUA), Greece) Despina Fotiou (Alexandra Hospital, National and Kapodistrian University, Athens Medical School, Greece) Efstathios Kastritis (National and Kapodistrian University of Athens, ) Meletios Dimopoulos (National and Kapodistrian University of Athens, Greece)

**Abstract:**

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**RESEARCH LETTER**

# Low Neutralizing Antibody Responses Against SARS-CoV-2 in Elderly Myeloma Patients After the First BNT162b2 Vaccine Dose

**Evangelos Terpos, MD[1]; Ioannis P. Trougakos, PhD[2]; Maria Gavriatopoulou, MD[1]; Ioannis Papassotiriou, PhD[3]; Aimilia D. Sklirou, PhD[2]; Ioannis Ntanasis-Stathopoulos, MD[1]; Eleni-Dimitra Papanagnou, PhD[2]; Despina Fotiou, MD[1]; Efstathios Kastritis, MD[1]; Meletios A. Dimopoulos, MD[1]**

**Author Affiliations:** [1]Department of Clinical Therapeutics, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece; [2]Department of Cell Biology and Biophysics, Faculty of Biology, National and Kapodistrian University of Athens, Athens, Greece; [3]Department of Clinical Biochemistry, "Aghia Sophia" Children's Hospital, Athens, Greece

**Corresponding author:** Evangelos Terpos, MD; Department of Clinical Therapeutics, National and Kapodistrian University of Athens, School of Medicine, Alexandra General Hospital, 80 Vas. Sofias Avenue, 11528, Athens, Greece; tel +30-213-216-2846; email: eterpos@med.uoa.gr

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Patients with multiple myeloma (MM) are at increased risk of infections due to their immunocompromised state, old age and comorbidities.[1] Coronavirus disease 2019 (COVID-19) causes moderate to severe acute respiratory dysfunction in 77% of MM patients and leads to critical condition approximately 8% of them.[2] More than 80% of MM patients who are infected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) require hospital admission,[3] while almost 33% of hospitalized MM patients with COVID-19 may die because of the infection [4]. This is mainly due to the limited therapeutic options for COVID-19 available to-date.[5]

Vaccination against SARS-CoV-2 could be an important preventive strategy against COVID-19 for MM patients, but its efficacy in MM is largely unknown.[6] The BNT162b2 mRNA vaccine is the first approved anti-SARS-CoV-2 vaccine by both US Food and Drug Administration and European Medicines Agency due to its high efficacy in apparently healthy adults.[7] Recently, it was reported that the first BNT162b2 dose provided some protection against COVID-19 among nursing facility members.[8,9] However, there is no information in the literature for the efficacy of BNT162b2 vaccine in patients with MM or with other malignant diseases. Herein, we report the development of neutralizing antibodies (NAbs) against SARS-CoV-2 in MM patients after the first dose of the BNT162b2 vaccine.

Major inclusion criteria for the participation of MM patients in this study included: (i) age above 18 years; (II) presence or smoldering myeloma or active MM, irrespective of the treatment given or the line of therapy; and (iii) eligibility for vaccination, according to International Myeloma Society recommendations[8]. Volunteers of similar age and gender, who served as controls, were also included in this analysis. Major exclusion criteria for both myeloma patients and controls included the presence of: (i) autoimmune disorder or active malignant disease; (ii) HIV or active hepatitis B and C infection and (iii) end-stage renal



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disease. Both patients and controls participate in a large prospective study (NCT04743388) for the kinetics of anti-SARS-CoV-2 antibodies after COVID-19 vaccination in healthy subjects and patients with hematological malignancies or solid tumors.

After vein puncture, serum of both patients and controls was collected on day 1 (D1; before the first BNT162b2 dose) and on day 22 (D22; before the second dose of the vaccine). Serum was separated within 4 hours from blood collection and stored at -80°C until the day of measurement. NAbs against SARS-CoV-2 were measured using FDA approved methodology (ELISA, cPass™ SARS-CoV-2 NAbs Detection Kit; GenScript, Piscataway, NJ, USA)[10] on the above timepoints. Samples of the same patient or control were measured in the same ELISA plate. The study was approved by the respective Ethical Committees in accordance with the Declaration of Helsinki and the International Conference on Harmonization for Good Clinical Practice. All patients and controls provided informed consent before entering into the study.

The current study population included 48 MM patients (29 males/19 females; median age: 83 years, range: 59-92 years) and 104 controls (57 males/47 females; median age: 83 years, range: 65-95 years), who were vaccinated during the same period, at the same vaccination center (Alexandra Hospital, Athens, Greece). The advanced age of the participants was due to the Greek vaccination program that prioritize octogenarians and health care workers for COVID-19 immunization.

The characteristics of myeloma patients are depicted in Table 1. In summary, at the time of vaccination, 35 (72.9%) patients were receiving anti-myeloma therapy, four were in remission after prior therapy and did not receive any therapy at the time of vaccination and nine had smoldering myeloma.



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On D1, no patient or control had NAb titers of ≥30% (the cut-off defining positivity); similarly, there was no difference regarding the NAb titers between MM patients and controls on D1. After the first dose of the vaccine, on D22, MM patients had lower NAb titers compared to controls: median NAb inhibition titers and range was 20.6% (0-96.7%) for MM patients versus 32.5% (5.2-97.3%) for controls; P<0.01; (Figure 1). More, specifically, only 12 (25.0%) MM patients versus 57 (54.8%) controls developed NAb titers ≥30% on D22. The respective number of MM patients and controls who developed NAb titers ≥50% (which corresponds to clinically relevant viral inhibition[11]) was 4 (8.3%) and 21 (20.2%), respectively. All these four MM patients were in remission, without receiving any anti-myeloma therapy; three after frontline therapy with bortezomib, lenalidomide and dexamethasone (VRd) [two patients were in very good partial response (VGPR) and one in partial response (PR) on the day of the administration of the first dose of the vaccine] and one patient after second line treatment with lenalidomide and dexamethasone (Rd) for 14 months (the patient was in VGPR on D1 of the vaccination). These four patients had also normal levels of the uninvolved immunoglobulins after treatment. No other correlation was observed between the anti-myeloma treatment given and the development of NAb titers on D22.

Interestingly, only one (11.1%) out of nine patients with smoldering myeloma had NAb titers of equal or more than 30% (positivity cut-off) versus 11/39 (28.2%) patients with active MM. This patient had normal levels of the univolved immunoglobulins, while the other eight patients had immunoparesis in at least one uninvolved immunoglobulin. This observation is of great interest as hypoglobulinemia has been associated with inferior antibody response among patients with chronic lymphocytic leukemia and COVID-19.[12]



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Our data indicate that the first dose of BNT162b2 leads to production of lower levels of NAbs against SARS-CoV-2 compared to non-MM controls of similar age and gender and without malignant disease. This may be due to the effect of myeloma cells which suppress normal B-cell expansion and immunoglobulin production. Furthermore, some anti-myeloma therapies have a B-cell depleting activity which in turn may impair immune response to vaccines, whereas both myeloma microenvironment and anti-myeloma treatments may impair T-cell function.[13] Patients with MM often present suboptimal seroconversion rates after a single-dose vaccine against bacteria and viruses and, therefore, booster doses are needed to assure adequate protection, such as in the case with the seasonal flu vaccine.[13] We should also take into consideration that the production of NAb titers against SARS-CoV-2 at a level of ≥50% on D21 after the first BNT162b2 dose has been low, even among healthy individuals aged 65-85 years.[11] However, higher antibody titers after a single dose of mRNA-based vaccine against SARS-CoV-2 have been detected in individuals who have recovered from COVID-19.[9] Since our results indicate that elderly myeloma patients have a blunted antibody response after the first vaccine dose, they also suggest that the administration of a second timely vaccine dose is essential for this elderly subpopulation, with a malignant hematological disease that deregulates the immune homeostasis, to develop an adequate antibody-based immune response. Anti-myeloma therapy seems to negatively affect the NAb production (after a single dose), although higher patient numbers are needed to evaluate the effects of specific anti-myeloma regimens on the immune responses of anti-SARS-CoV-2 vaccination. Furthermore, this low antibody response of elderly myeloma patients after the first BNT162b2 dose may not be seen in younger patients. Our ongoing study will answer this question also.



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**Conflicts of interest:** The authors declare no relevant conflict of interest for this study.

**Author Contribution Statement:** ET designed research, performed research, analyzed data and wrote the paper; IPT and MAD contributed vital new reagents or analytical tools, performed research, analyzed data, reviewed all paper drafts and gave approval to final version; IP, ADS, IN-S, E-DP, DF and EK performed research, analyzed data, reviewed all paper drafts and gave approval to final version.

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**References**


1. Dumontet C, Hulin C, Dimopoulos MA, et al. A predictive model for risk of early grade >/= 3 infection in patients with multiple myeloma not eligible for transplant: analysis of the FIRST trial. *Leukemia*. 2018;32(6):1404-1413.

2. Martinez-Lopez J, Mateos MV, Encinas C, et al. Multiple myeloma and SARS-CoV-2 infection: clinical characteristics and prognostic factors of inpatient mortality. *Blood Cancer J*. 2020;10(10):103.

3. Engelhardt M, Shoumariyeh K, Rosner A, et al. Clinical characteristics and outcome of multiple myeloma patients with concomitant COVID-19 at Comprehensive Cancer Centers in Germany. *Haematologica*. 2020;105(12):2872-2878.

4. Chari A, Samur MK, Martinez-Lopez J, et al. Clinical features associated with COVID-19 outcome in multiple myeloma: first results from the International Myeloma Society data set. *Blood*. 2020;136(26):3033-3040.

5. Gavriatopoulou M, Ntanasis-Stathopoulos I, Korompoki E, et al. Emerging treatment strategies for COVID-19 infection. *Clin Exp Med*. 2020.

6. Gavriatopoulou M, Ntanasis-Stathopoulos I, Korompoki E, Terpos E, Dimopoulos MA. SARS-CoV-2 Vaccines in Patients With Multiple Myeloma. *Hemasphere*. 2021;5(3):e547.

7. Polack FP, Thomas SJ, Kitchin N, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N Engl J Med*. 2020;383(27):2603-2615.

8. Gharpure R, Patel A, Link-Gelles R. First-Dose COVID-19 Vaccination Coverage Among Skilled Nursing Facility Residents and Staff. *JAMA*. 2021.


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9. Saadat S, Tehrani ZR, Logue J, et al. Binding and Neutralization Antibody Titers After a Single Vaccine Dose in Health Care Workers Previously Infected With SARS-CoV-2. *JAMA*. 2021.

10. Tan CW, Chia WN, Qin X, et al. A SARS-CoV-2 surrogate virus neutralization test based on antibody-mediated blockage of ACE2-spike protein-protein interaction. *Nat Biotechnol*. 2020;38(9):1073-1078.

11. Walsh EE, Frenck RW, Jr., Falsey AR, et al. Safety and Immunogenicity of Two RNA-Based Covid-19 Vaccine Candidates. *N Engl J Med*. 2020;383(25):2439-2450.

12. Roeker LE, Knorr DA, Pessin MS, et al. Anti-SARS-CoV-2 antibody response in patients with chronic lymphocytic leukemia. *Leukemia*. 2020;34(11):3047-3049.

13. Ludwig H, Boccadoro M, Moreau P, et al. Recommendations for vaccination in multiple myeloma: a consensus of the European Myeloma Network. *Leukemia*. 2021;35(1):31-44.

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**Table 1. Characteristics of patients with multiple myeloma**

| | |
|---|---|
| **Number of patients (M/F)** | **48 (29/19)** |
| **Age in years, median (range)** | **83 (59-92)** |
| **Smoldering Myeloma/Active Myeloma, n (%)** | **9 (18.7) / 39 (81.2)** |
| **On treatment for Active Myeloma (n=39), Yes/No** | **35/4** |
| **Line of therapy, If on treatment, n (% of 35 patients)** | |
| 1st line | 15 (42.8) |
| 2nd line | 10 (28.5) |
| 3rd line | 4 (11.4) |
| >3rd line | 6 (17.1) |
| Type of therapy, n (%) | |
| **PI+IMiD combos** | **9 (25.7)** |
| VRD | 6 |
| IRD | 2 |
| PomVD | 1 |
| **IMiD-based regimens** | **14 (40.0)** |
| Rd | 10 |
| R-maintenance | 2 |
| RCd | 1 |
| PomCd | 1 |
| **PI-based regimens** | **2 (5.7)** |
| VD | 1 |
| ICD | 1 |
| **Anti-CD38- MAb-based therapies** | **8 (22.8)** |
| Daratumumab monotherapy | 4 |
| Daratumumab-Rd | 2 |
| Daratumumab-PomDex | 1 |
| Isatuximab-Rd | 1 |
| **Belantamab mafodotin monotherapy** | **2 (5.7)** |

Abbreviations: PI: proteasome inhibitor; IMiD: immunomodulatory drug; VRD, bortezomib, lenalidomide and dexamethasone; IRD, ixazomib, lenalidomide and dexamethasone; PomVD: pomalidomide, bortezomib and dexamethasone; Rd, lenalidomide and dexamethasone; R, lenalidomide; RCD, lenalidomide, cyclophosphamide and



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dexamethasone; PomCd, pomalidomide, cyclophosphamide and dexamethasone; VD, bortezomib and dexamethasone; ICD, ixazomib, cyclophosphamide and dexamethasone

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**Figure legend**

**Figure 1. Kinetics of neutralizing antibodies in elderly myeloma patients and age-matched controls after vaccination with the first dose of the BNT162b2 mRNA vaccine.**

On D22, myeloma patients had lower production of NAb inhibition titers compared to controls of similar age and gender (see text). Only four myeloma patients had NAb titers of equal or more than 50%.

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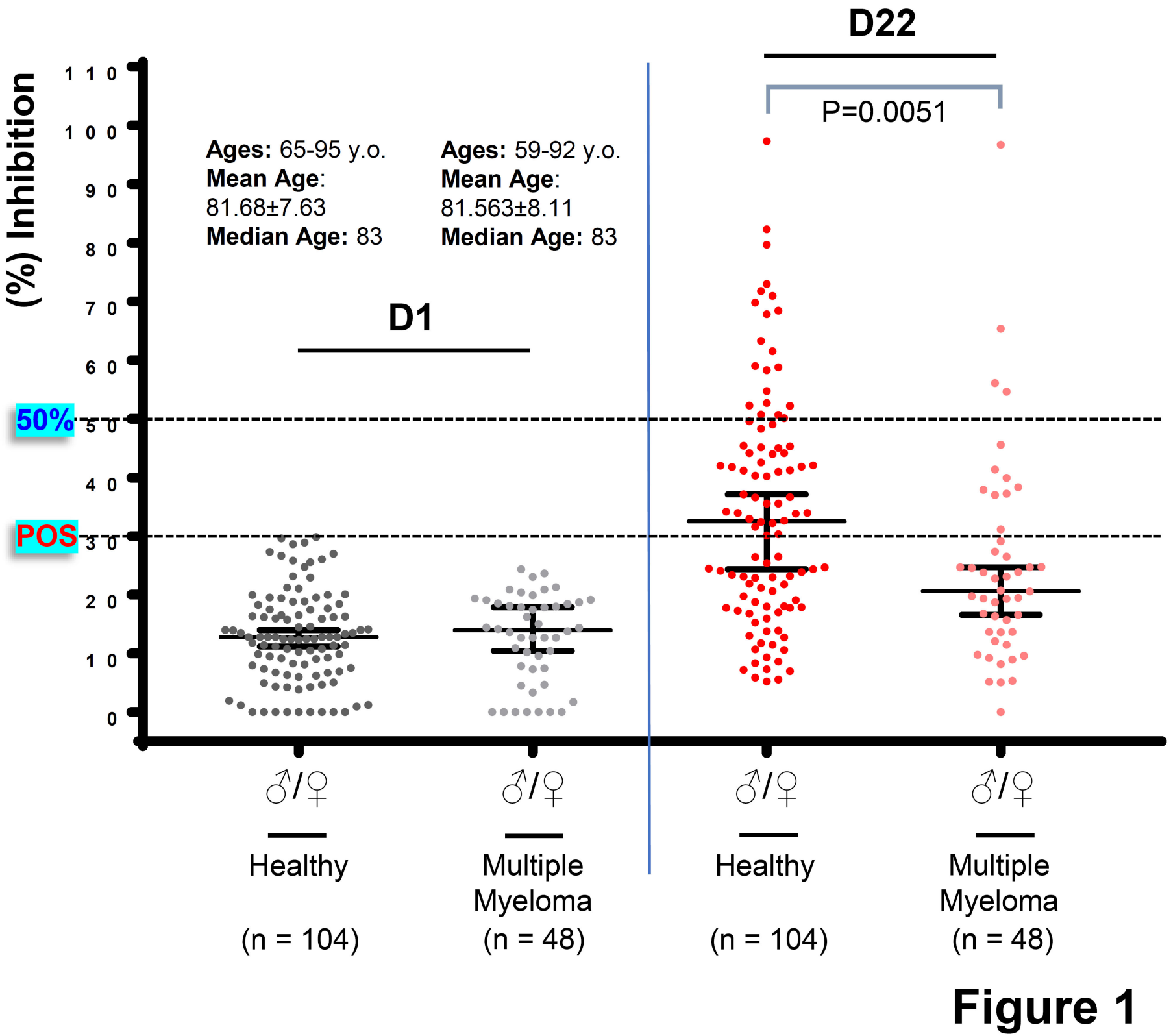


**Figure 1**

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