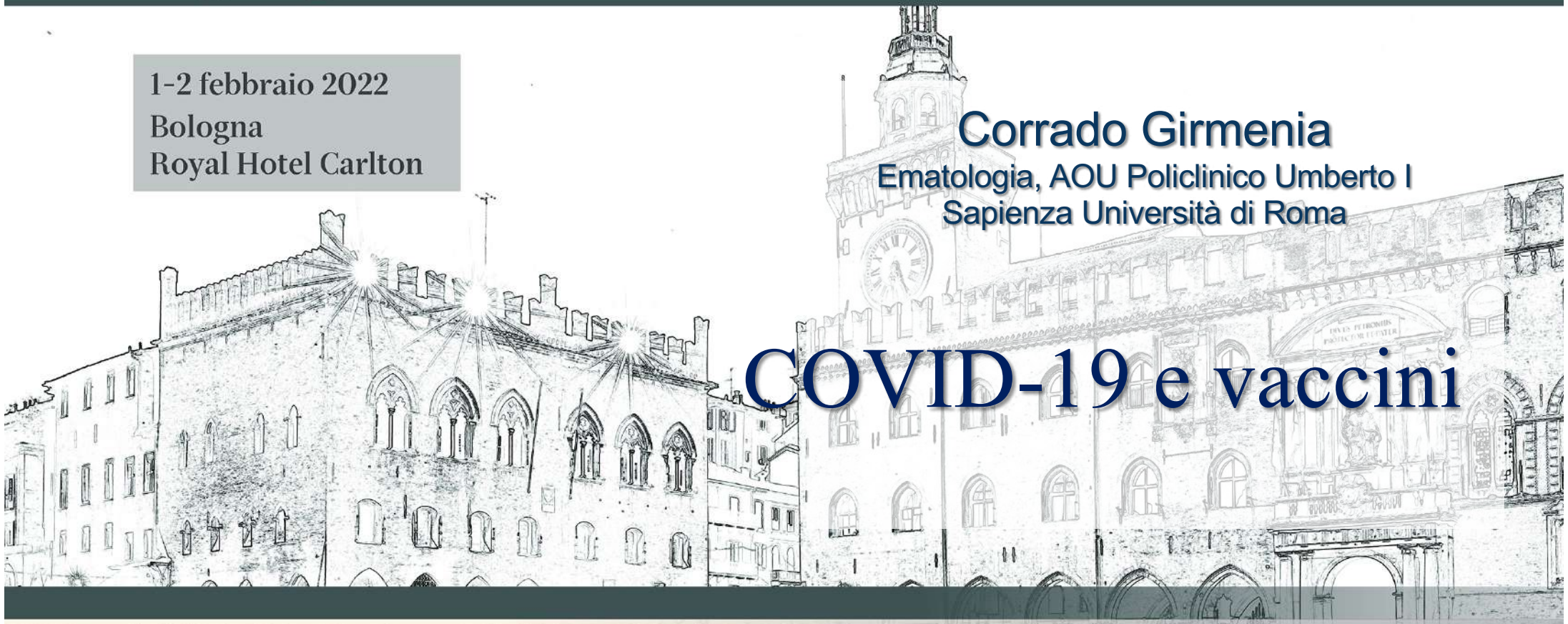
Highlights from IMW 2021

1-2 febbraio 2022
Bologna
Royal Hotel Carlton



Corrado Girmenia
Ematologia, AOU Policlinico Umberto I
Sapienza Università di Roma

COVID-19 e vaccini

Lancet Haematol 2021;
8: e934–46

COVID-19 vaccination in patients with multiple myeloma: a consensus of the European Myeloma Network

Heinz Ludwig, Pieter Sonneveld, Thierry Facon, Jesus San-Miguel, Hervé Avet-Loiseau, Mohamad Mohty, Maria-Victoria Mateos, Philippe Moreau, Michele Cavo, Charlotte Pawlyn, Sonja Zweegman, Monika Engelhardt, Christoph Driessen, Gordon Cook, Melitios A Dimopoulos, Francesca Gay, Hermann Einsele, Michel Delforge, Jo Caers, Katja Weisel, Graham Jackson, Laurent Garderet, Niels van de Donk, Xavier Leleu, Hartmut Goldschmidt, Meral Beksac, Inger Nijhof, Martin Schreder, Niels Abildgaard, Roman Hajek, Niklas Zojer, Efstathios Kastritis, Annemiek Broijl, Fredrik Schjesvold, Mario Boccadoro, Evangelos Terpos

Panel: Summary of recommendations from the European Myeloma Network for vaccination against SARS-CoV-2

The European Myeloma Network recommends that all patients with monoclonal gammopathy of unknown significance, smouldering multiple myeloma, multiple myeloma, and monoclonal gammopathies of clinical significance should be vaccinated with a COVID vaccine

Patients should be vaccinated preferably

- Before onset of active multiple myeloma
- During well controlled disease at times of minimal residual disease negativity, complete response, or very good partial response
- Before start of therapy, before stem-cell collection, and more than 3 months after autologous haematopoietic stem-cell transplantation
- During periods without therapy (exception: lenalidomide maintenance therapy)
- Vaccination might be considered on individual judgment in patients with poorly controlled disease or ongoing therapy, but induction of protective immune response is less likely
- Patients with previously confirmed COVID-19 infection should be vaccinated as well (one dose might be sufficient)

Consider risk factors for poor response

- Uncontrolled disease
- Immunoparesis
- Number of previous lines of therapy
- Age, certain treatments (eg, anti-CD38 antibodies and B cell maturation antigen-targeted therapy, including bi-specific T-cell engagers and chimeric antigen receptor T-cell therapy)

Routine evaluation of the immune response to vaccination is not supported by the Centers for Disease Control and Prevention and other organisations but allows identification of patients without any or with low anti-SARS-CoV-2 immune response

In case of immune impairment

- Administer a third vaccine dose
- Insufficiently protected patients should comply with principles for infection risk reduction
- Those patients will depend on herd immunity and will benefit from so-called ring vaccination of partners and close social contacts
- Administration of protective monoclonal antibodies might be considered in immunosuppressed patients who contract or have been exposed to COVID-19
- Health-care personnel caring for patients with multiple myeloma and household members should be vaccinated

Efficacy of COVID-19 Vaccination in patients with multiple myeloma: key questions

- Rate of response to vaccination
- Differences according to phase of disease and treatment
- Response in pts with pre-vaccination COVID-19
- Risk and outcome of breakthrough COVID-19
- Message to patients

Literature review

18th International Myeloma Workshop

63rd ASH Annual Meeting and Exposition

Pimpinelli et al. J Hematol Oncol (2021) 14:81
https://doi.org/10.1186/s13045-021-01090-6

Journal of Hematology & Oncology

RESEARCH Open Access

Fifth-week immunogenicity and safety of anti-SARS-CoV-2 BNT162b2 vaccine in patients with multiple myeloma and myeloproliferative malignancies on active treatment: preliminary data from a single institution

Fulvia Pimpinelli[1], Francesco Marchesi[2*], Giulia Piaggio[3], Diana Giannarelli[4], Elena Papa[2], Paolo Falcucci[2], Martina Pontone[1], Simona Di Martino[3], Valentina Laquintana[5], Antonia La Malfa[6], Enea Gino Di Domenico[1], Ornella Di Bella[7], Gianluca Falzone[2], Fabrizio Ensoli[1], Branka Vujovic[7], Aldo Morrone[8], Gennaro Ciliberto[3] and Andrea Mengarelli[2]

42 patients with MM all of them on active anti-cancer treatment. At 5 weeks, GMC of IgG in elderly controls was 353.3 AU/mL versus 106.7 in MM (p = 0.003). Seroprotection rate at cutoff of 15 AU/mL was 100% in controls compared to **78.6% in MM** (p = 0.003).

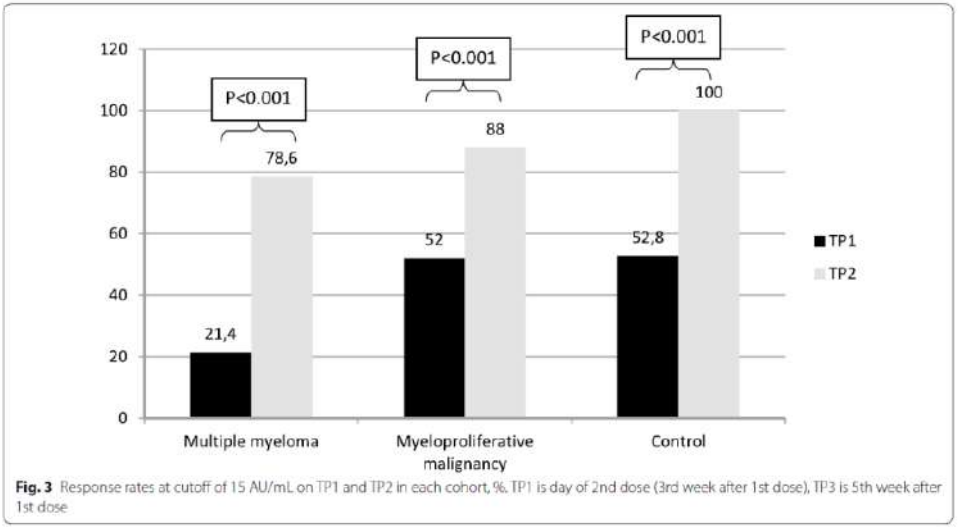


Fig. 3 Response rates at cutoff of 15 AU/mL on TP1 and TP2 in each cohort, %. TP1 is day of 2nd dose (3rd week after 1st dose), TP3 is 5th week after 1st dose

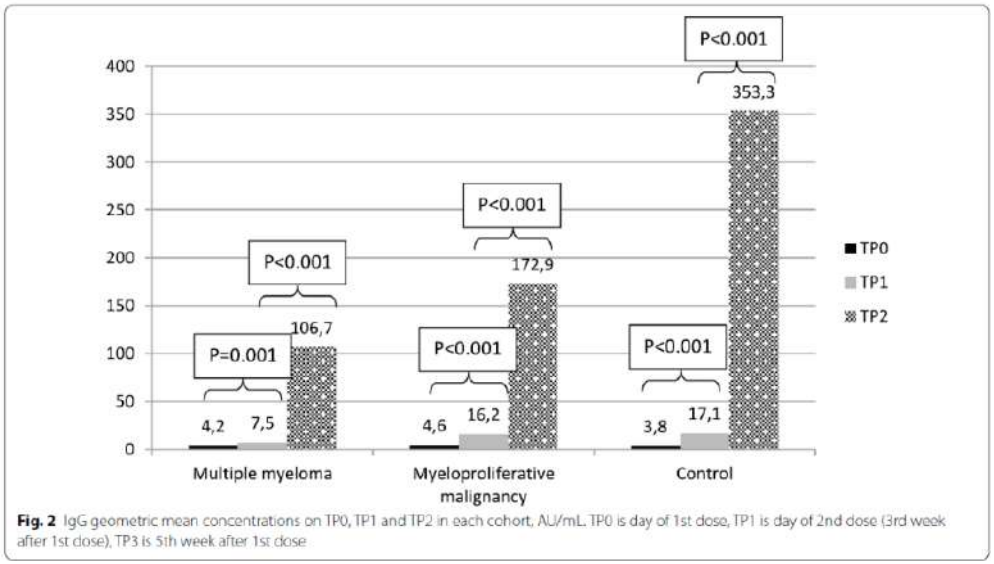


Fig. 2 IgG geometric mean concentrations on TP0, TP1 and TP2 in each cohort, AU/mL. TP0 is day of 1st dose, TP1 is day of 2nd dose (3rd week after 1st dose), TP3 is 5th week after 1st dose

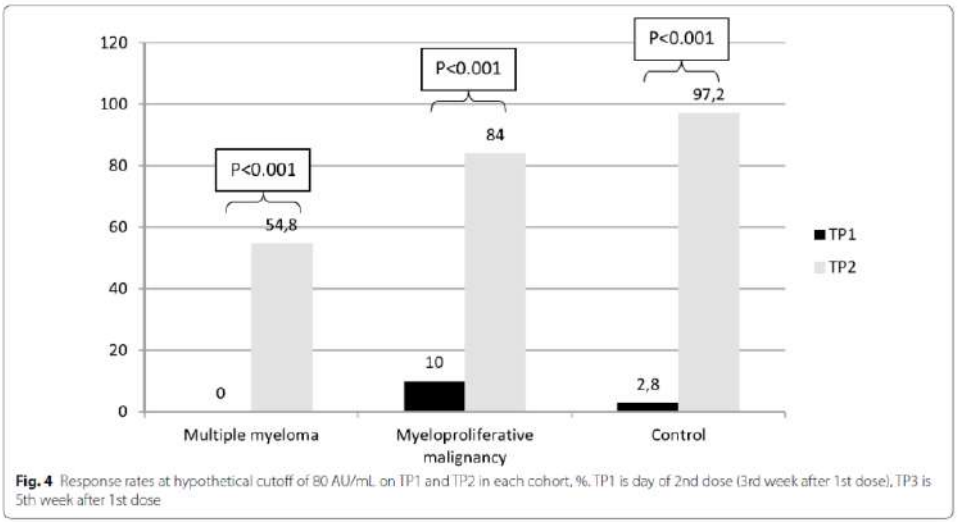


Fig. 4 Response rates at hypothetical cutoff of 80 AU/mL on TP1 and TP2 in each cohort, %. TP1 is day of 2nd dose (3rd week after 1st dose), TP3 is 5th week after 1st dose

Humoral response rate and predictors of response to BNT162b2 mRNA COVID19 vaccine in patients with multiple myeloma

bjh BRITISH JOURNAL OF HAEMATOLOGY

Irit Avivi,[1,2] Roi Balaban,[1] Tamir Shragai,[1,2] Gabi Sheffer,[1] Miguel Morales,[1] Anat Aharon,[1] Noa Lowenton-Spier,[1] Svetlana Trestman,[1] Chava Perry,[1,2] Noam Benyamini,[1,2] Moshe Mittelman,[1,2] Yaara Tabib,[1,2] Tali Bar Lev,[1,2] Mor Zavaro,[1,2] Yair Herishanu,[1,2] Efrat Luttwak[1,2] and Yael C. Cohen[1,2]

This single-centre prospective study included 171 MM patients tested for serological response 14–21 days post second vaccine. 64 vaccinated healthy volunteers served as controls.

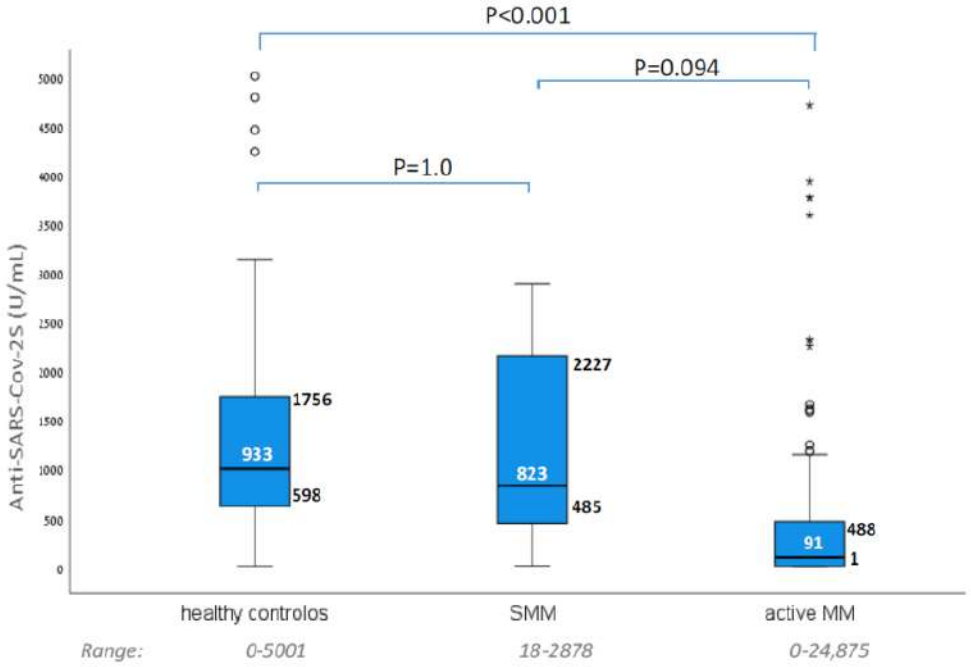
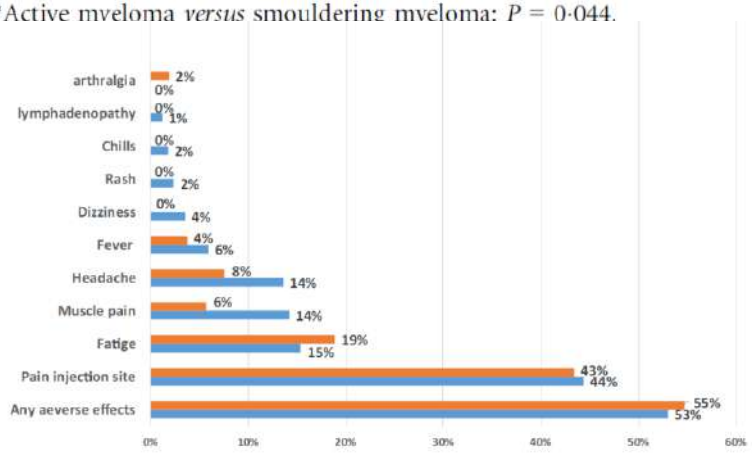


Table II. Rate of serological response to BNT162b2 vaccine.

Cohort	Antibody response *n* (%) Positive	Negative	*P* value vs. healthy controls
Healthy controls	63 (98)	1 (2)	
All myeloma	133 (78)	38 (22)	0·000132
Active myeloma*	121 (76)	38 (24)	0·00062
Smoldering myeloma*	12 (100)	0 (0)	0·722

*Active myeloma *versus* smouldering myeloma: $P = 0·044$.



Response to mRNA vaccination for COVID-19 among patients with multiple myeloma

Leukemia. 2021 Jul 29:1-8.

Samuel D. Stampfer[1], Marissa-Skye Goldwater[2], Scott Jew[2], Sean Bujarski[2], Bernard Regidor[3], David Daniely[2], Haiming Chen[2], Ning Xu[2], Mingjie Li[2], Tracy Green[3], Eddie Fung[3], Elias Aquino[3], Regina Swift[3], Shahrooz Eshaghian[4], Kurt Preugschat[5], Aaron J. Feinstein[6,7], Tanya M. Spektor[8] and James R. Berenson[2,3,8]

Using an ELISA-based assay that detects IgG antibodies to SARS-CoV-2 spike protein, we determined serum antibody levels prior to immunization and 12–21 and 14–21 days following the first and second vaccinations, respectively, with mRNA-1273 (Moderna) or BNT162b2 (Pfizer/BioNTech) among 103 MM patients (96 and 7 with active and smoldering disease, respectively). We stratified patients into clinically relevant responders (>250 IU/mL), partial responders (50–250 IU/mL, which was above pre-COVID-19 background), and nonresponders (<50 IU/mL).

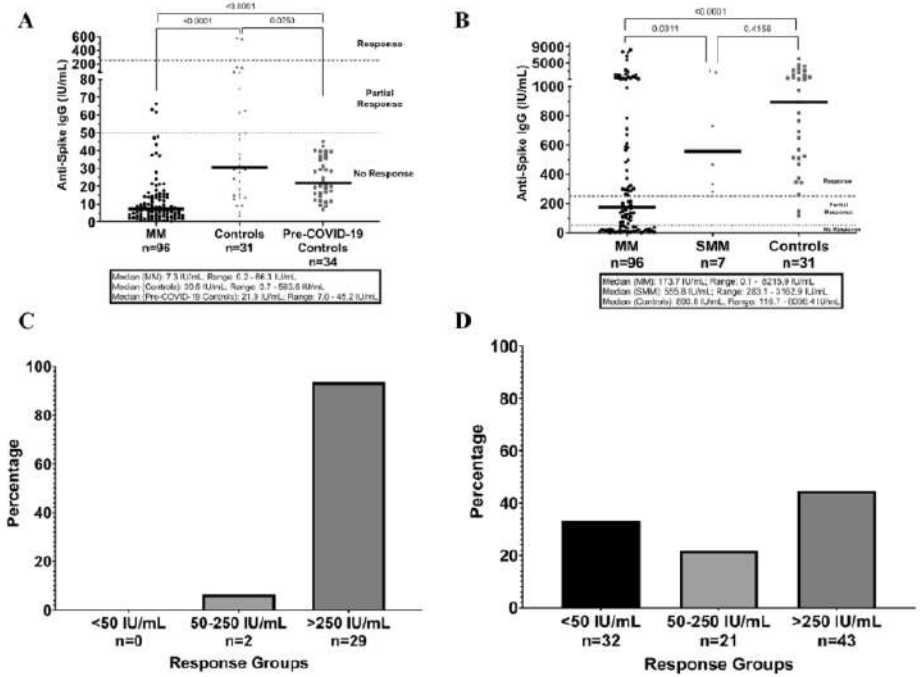


Fig. 1 Anti-SARS-CoV-2 spike IgG levels. Anti-SARS-CoV-2 spike IgG levels were measured prior to vaccination (**A**) in multiple myeloma patients (MM), age-matched controls, and separately tested on banked sera from before the COVID-19 era. Postvaccination IgG levels were drawn 14–21 days after the second dose (**B**) in MM, smoldering multiple myeloma (SMM), and age-matched healthy subjects. Participants were stratified as nonresponders if they did not exceed pre-COVID-19 antibody levels (50 IU/mL, lower dotted line), partial responders if they failed to exceed the bottom 6th percentile of healthy controls (250 IU/mL, upper dashed line), and clinically significant responders if above 250 IU/mL. Relative percentages of controls (**C**) and MM patients (**D**) fell into these three distinct groups.

Leukemia. 2021 Jul 29:1-8.

Response to mRNA vaccination for COVID-19 among patients with multiple myeloma

Samuel D. Stampfer[1], Marissa-Skye Goldwater[2], Scott Jew[2], Sean Bujarski[2], Bernard Regidor[3], David Daniely[2], Haiming Chen[2], Ning Xu[2], Mingjie Li[2], Tracy Green[3], Eddie Fung[3], Elias Aquino[3], Regina Swift[3], Shahrooz Eshaghian[4], Kurt Preugschat[5], Aaron J. Feinstein[6,7], Tanya M. Spektor[8] and James R. Berenson[2,3,8]

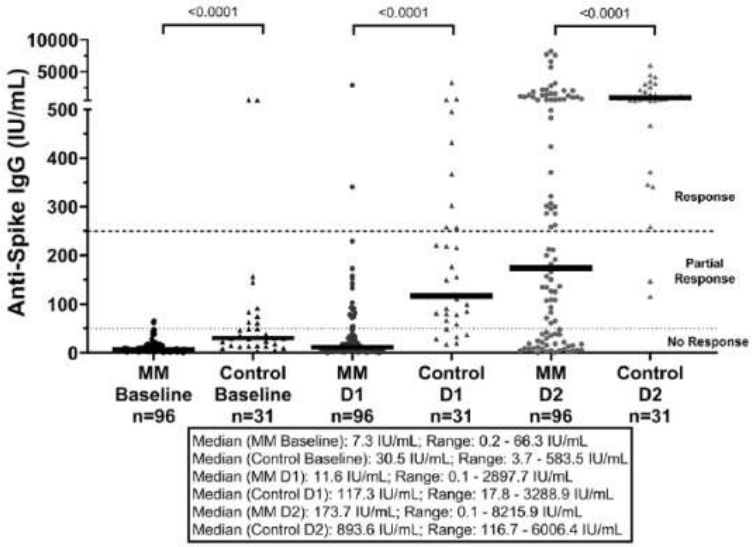


Fig. 2 Comparison of anti-SARS-CoV-2 spike IgG levels between controls and MM patients. Anti-SARS-CoV-2 spike IgG levels measured at baseline, D1 (12–21 days after first dose of vaccine), and D2 (14–21 days after second dose). The lower dotted line at 50 IU/mL is the cutoff between nonresponse and partial response, with the upper dashed line at 250 IU/mL as the cutoff to achieve an expected clinically significant response.

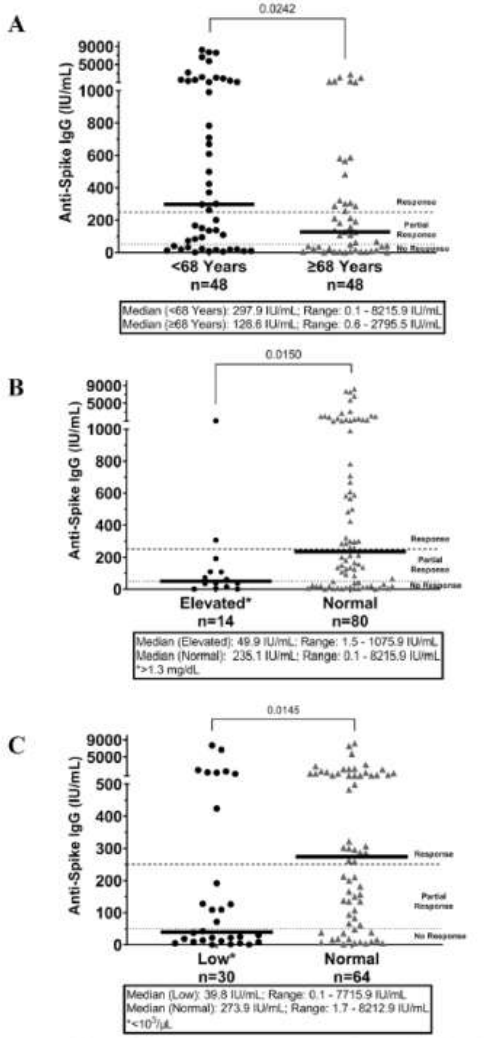


Fig. 3 Correlation between anti-SARS-CoV-2 spike IgG levels and demographic and clinical characteristics. D2 anti-spike IgG levels were stratified by age above or below the median (**A**), creatinine at an elevated level of >1.3 mg/dL vs normal (**B**), and low lymphocyte count $<10^3$/μL vs normal (**C**). Dotted and dashed lines indicate 50 and 250 IU/mL.

Age

Creatinine level

Lymphocyte count

Blood Cancer Journal (2021)11:138;

The neutralizing antibody response post COVID-19 vaccination in patients with myeloma is highly dependent on the type of anti-myeloma treatment

Evangelos Terpos[1], Maria Gavriatopoulou[1], Ioannis Ntanasis-Stathopoulos[1], Alexandros Briasoulis[1], Sentiljana Gumeni[2],

18th International Myeloma Workshop September 8 - 11, 2021 - Vienna, Austria

P-127 Patients With Multiple Myeloma on Treatment with Anti-CD38 or Anti-BCMA Agents Have a Suboptimal Humoral Response Following COVID-19 vaccination. Terpos et al

- Importantly, active treatment with either anti-CD38 monoclonal antibodies or belantamab mafodotin and lymphopenia at the time of vaccination were independent prognostic factors for suboptimal antibody response following vaccination (OR: 9.4, 95% CI: 1.7-51.1, p=0.009, OR 2.9, 95% CI: 1.2-7.1, p=0.002 and OR: 3.5, 95% CI: 1.8-6.7, p=0.019, respectively)

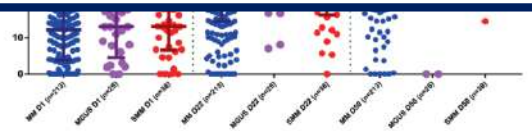


Fig. 3 Kinetics of NAbs in MM compared with SMM and MGUS after vaccination with 2 doses of the BNT162b2 or 1 dose of the AZD1222 vaccine. A statistically significant difference was identified both on day 22 and day 50 between the MM and MGUS group.

especially under treatment with anti-CD38 or belantamab. This underlines the need for timely vaccination, possibly during a treatment-free period, and for continuous vigilance on infection control measures in non-responders.

bjh BRITISH JOURNAL OF HAEMATOLOGY

Myeloma patients with COVID-19 have superior antibody responses compared to patients fully vaccinated with the BNT162b2 vaccine

Serum was collected either four weeks post confirmed diagnosis or four weeks post a second dose of BNT162b2.

Maria Gavriatopoulou,[1] Evangelos Terpos,[1] Panagiotis Malandrakis,[1] Ioannis Ntanasis-Stathopoulos,[1] Alexandros Briasoulis,[1] Sentiljana Gumeni,[2] Despina Fotiou,[1] Eleni-Dimitra Papanagnou,[2] Magdalini Migkou,[1] Foteini Theodorakakou,[1] Evangelos Eleutherakis-Papaiakovou,[1] Nikolaos Kanellias,[1] Ioannis P. Trougakos,[2] Efstathios Kastritis[1] and Meletios-Athanasios Dimopoulos[1]

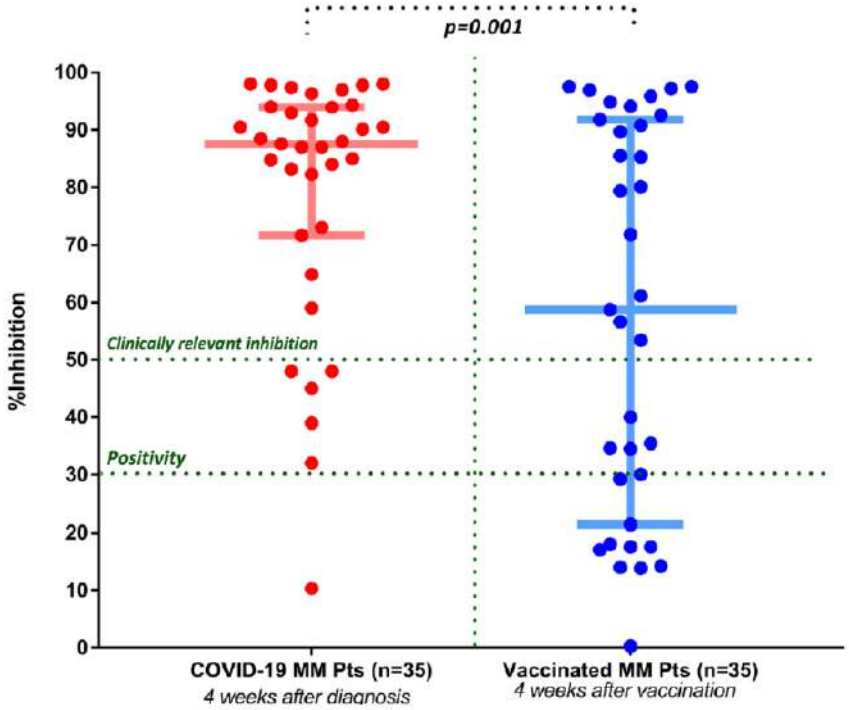


Fig 1. Patients with MM and COVID-19 showed a superior humoral response compared with vaccinated patients with MM. The median (IQR) NAb titre was 87·6% and 58·7% for COVID-19-positive and vaccinated patients (P = 0·01). IQR, interquartile range; MM, multiple myeloma; NAb, neutralizing antibody. [Colour figure can be viewed at wileyonlinelibrary.com]

Importantly, there was no difference in NAb production between COVID-19-positive and vaccinated patients who did not receive any treatment (median NAb 851% vs 917%, P = 014).

18th International Myeloma Workshop
September 8 - 11, 2021 - Vienna, Austria

- OAB-045 COVID-19 Vaccine Responsiveness in Patients with Multiple Myeloma and Waldenström Macroglobulinemia. Andrew Branagan et al
  - Primary endpoint is S antibody detection 28 days after final vaccination.
  - S antibody response rate was **91% (83/91) in MM** and **60% (27/45) in WM**. However, response rates for achieving S antibody >100 U/mL were **56% (51/91) in MM** and **33% (15/45) in WM.**
  - Vaccine-specific S antibody responses following **mRNA-1273**, **BNT162b2**, and **JNJ-78436735** were 74% (25/34; $p<0.05$), 51% (24/47; p=NS), and 20% (2/10; $p<0.05$) in MM and 67% (10/15; $p<0.005$), 19% (5/27; $p<0.05$), and 0% (0/3; p=NS) in WM.
  - Among MM patients with progressive disease, S antibody response >100 u/mL occurred in **45% (9/20)** as opposed to **65% (35/54)** for VGPR+ . Among **WM patients**, S antibody responses >100 U/mL occurred in 73% (8/11) ($p<0.05$) previously untreated; 0% (0/8) ($p<0.05$) received rituximab within 12 months; 15% (3/20) ($p<0.05$) on an active Bruton Tyrosine Kinase (BTK) inhibitor;

Suboptimal humoral immune response to SARS-CoV-2 mRNA vaccination in myeloma patients is associated with anti-CD38 mAb and BCMA-targeted treatment.

O. Van Oekelenel al . Icahn School of Medicine at Mount Sinai, New York, NY, USA.

18th International Myeloma Workshop; 63rd ASH Annual Meeting and Exposition

Study design and cohort

MARS study (Myeloma Antibody Response Study)

- **Goal:** characterize **humoral** and **cellular immune response** to **SARS-CoV-2 vaccine** in **MM patients**
  - >300 patients enrolled (11/2021)
  - Longitudinal collection of blood + saliva
  - Detailed clinical annotation
  - High-dimensional immune phenotyping in subset
- Supplemented with retrospective data from MM patients treated at Mount Sinai, NY, for which anti-spike IgG available

Study design and cohort

MARS study (Myeloma Antibody Response Study)

- **Cohort presented here:**
  - **431 MM patients in total** (incl. 34 SMM patients)
  - 421 (98%) had **2 doses of mRNA vaccine** recorded
  - 399 (93%) with available anti-spike IgG >10 days after **second** dose of mRNA vaccine
  - 207 (48%) had **"third dose" of vaccine** recorded
  - 131 (30%) with available anti-spike IgG >7 days after **third** dose of (mRNA) vaccine
  - **T cell data** for a subset of 44 MM patients (10%), more currently being analyzed

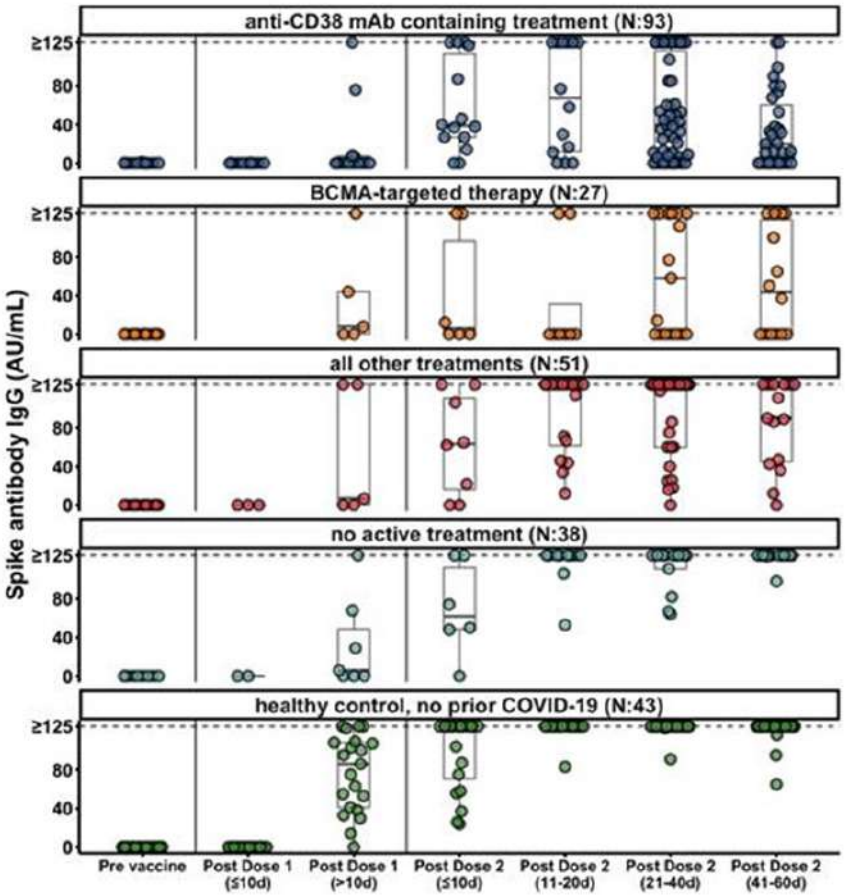
	Total N = 431
Age (y), median (range)	67 (37-93)
Male gender, % (n)	56% (240)
BNT162b2 (Pfizer) vaccine, % (n)	71% (306)
Heterologous vaccination, % (n)	8% (15/181)
Time of dose 3 after dose 1 (d), median (range)	224 (69-281)
Had COVID-19, % (n)	17% (73)
SMM, % (n)	8% (34)
Time since diagnosis, mo (range)	58 (0-254)
Prior lines of treatment, median (range)	2 (0-16)
(s)CR at time of first vaccine, % (n)	40% (173)

Blood and saliva were taken at multiple time points and compared with serology data of 69 age-matched vaccinated healthcare workers. We profiled SARS-CoV-2-specific T cell responses in a subset of 45 MM patients and 12 age-matched healthy controls by flow cytometry and ELIspot.

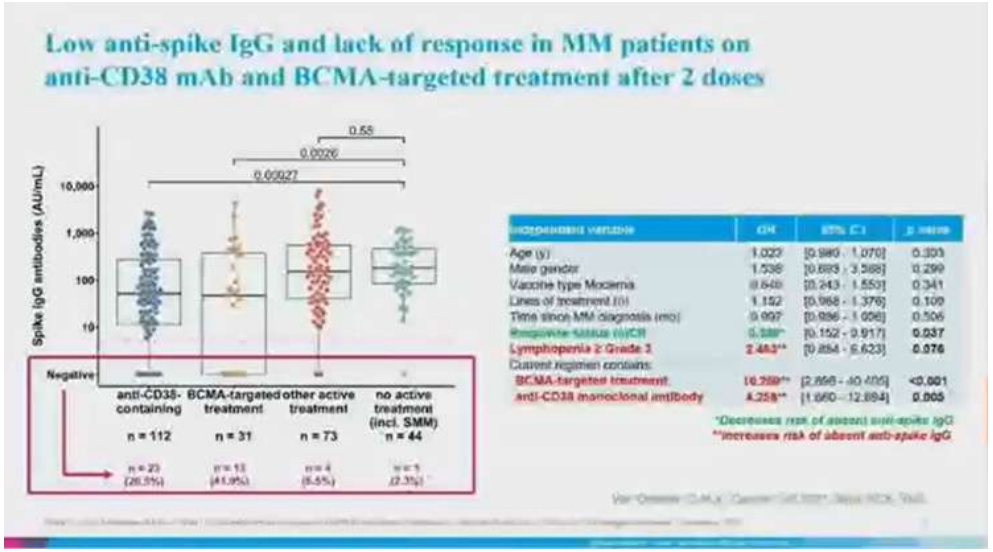
Suboptimal humoral immune response to SARS-CoV-2 mRNA vaccination in myeloma patients is associated with anti-CD38 mAb and BCMA-targeted treatment.

O. Van Oekelenel al . Icahn School of Medicine at Mount Sinai, New York, NY, USA.

18th International Myeloma Workshop; 63rd ASH Annual Meeting and Exposition



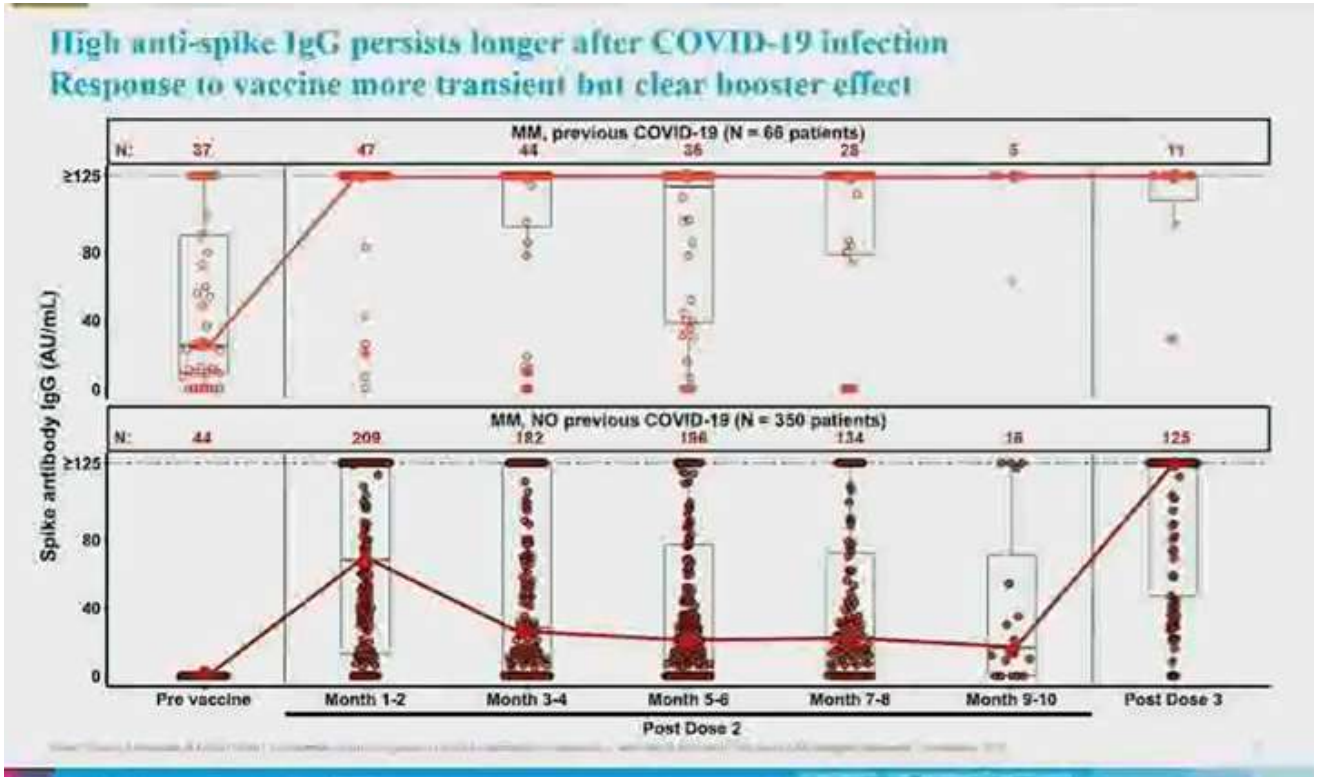
- Repeat Ab measurements up to 60 days after second vaccination confirm delayed and suboptimal IgG kinetics, particularly in patients receiving anti-MM treatment compared to controls
- Multivariate analysis (corrected for age, vaccine type, lines of treatment, time since diagnosis, response status and lymphopenia) confirmed that anti-CD38 (p=0.005) and BCMA-targeted treatment (p<0.001) are associated with not developing detectable anti-S IgG.



Suboptimal humoral immune response to SARS-CoV-2 mRNA vaccination in myeloma patients is associated with anti-CD38 mAb and BCMA-targeted treatment.

O. Van Oekelenel al . Icahn School of Medicine at Mount Sinai, New York, NY, USA.

18th International Myeloma Workshop; 63rd ASH Annual Meeting and Exposition



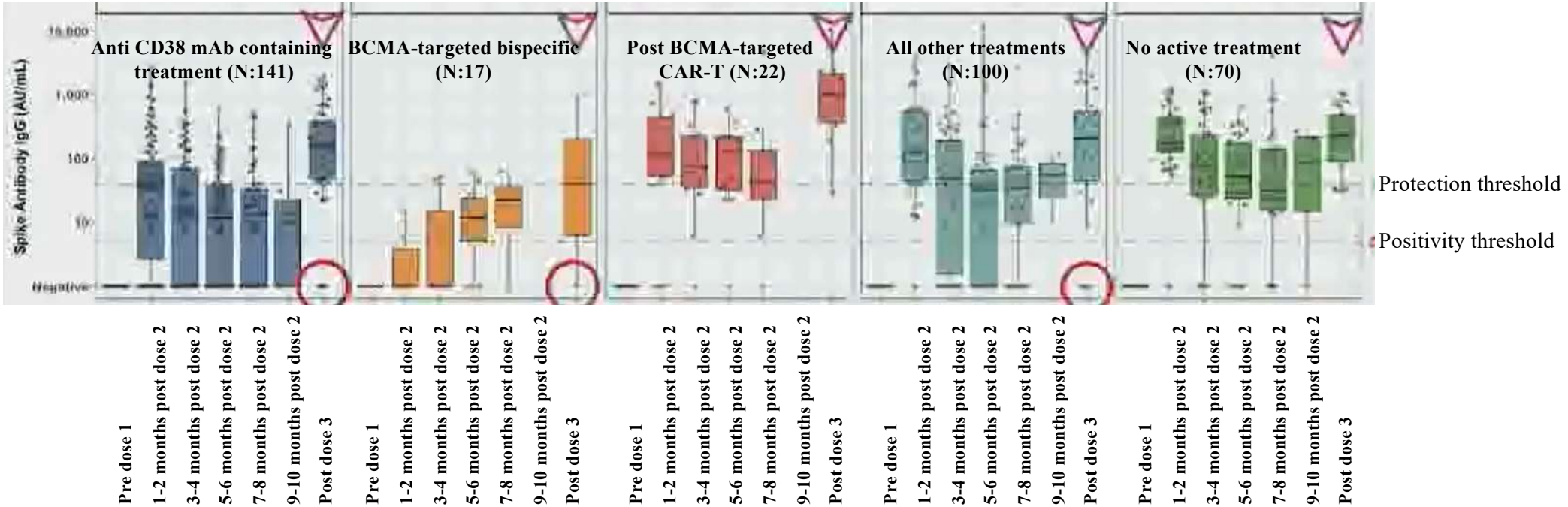
- Out of 43 MM pts with no detectable anti-Spike IgG after 2 doses 34 (81%) developed detectable IgG levels after third dose (median increase, 0 -> 58 AU/ml)
- Of 23 pts under anti-CD38 containing regimens and not responding after 2 doses, 19 (83%) responded to third dose
- Out of 79 MM pts with detectable anti-Spike IgG after 2 doses 78 (99%) incresded IgG levels after third dose (median increase, 34 -> 382 AU/ml).

Suboptimal humoral immune response to SARS-CoV-2 mRNA vaccination in myeloma patients is associated with anti-CD38 mAb and BCMA-targeted treatment.

O. Van Oekelenel al . Icahn School of Medicine at Mount Sinai, New York, NY, USA.

18th International Myeloma Workshop; 63rd ASH Annual Meeting and Exposition

Anti-CD38 mAb and BCMA bispecific impact durability but third dose vaccination effect observed across all cohorts



- Patients on treatment with anti-CD38 mAb lose detectable anti-spike IgG faster than other MM patients
- Patients with BCMA bispecific Ab (n=17) demonstrate persistently low anti-spike IgG in our cohort
- 5 patients (6%) persistently negative after 3 doses

Suboptimal humoral immune response to SARS-CoV-2 mRNA vaccination in myeloma patients is associated with anti-CD38 mAb and BCMA-targeted treatment.

O. Van Oekelenel al . Icahn School of Medicine at Mount Sinai, New York, NY, USA.

18th International Myeloma Workshop; 63rd ASH Annual Meeting and Exposition

Summary and conclusions

- **SARS-COV-2 anti-spike IgG response is suboptimal and highly variable in MM patients after 2 doses of mRNA vaccination.**
- **Prior COVID-19 infection associated with higher and more durable IgG response**
- **Significant fraction (15%) does not develop any detectable anti-spike IgG (non-responders) after 2 doses (significant association with anti-CD38 mAb and BCMA-targeted therapy, response status and lymphopenia.**
- **Lack of IgG response associated with weaker SARS-CoV-2-specific T cell response**
- **Third dose leads to sero-conversion in majority (81%) of non responders, but 19% persistently negative, more data to be collected.**
- **Third dose leads to sero-elevation in virtually responders.**

- Among 1182 vaccinated patients with MM 187 were diagnosed with SARS-CoV-2 breakthrough infection. The overall risk of SARS-CoV-2 breakthrough infections was 15.4% in the MM population and 3.9% in the noncancer population.
- After propensity score matching for demographics, adverse socioeconomic determinants of health, transplant procedures, comorbidities, vaccine types, and medications, patients with MM remained at significantly increased risk for breakthrough infections compared with matched patients without cancer **(HR, 1.34; 95%CI, 1.06-1.69).**
- The estimated probability of hospitalization at the end of the time window (October 8, 2021) was 34.4% for patients withMM

JAMA Network Open

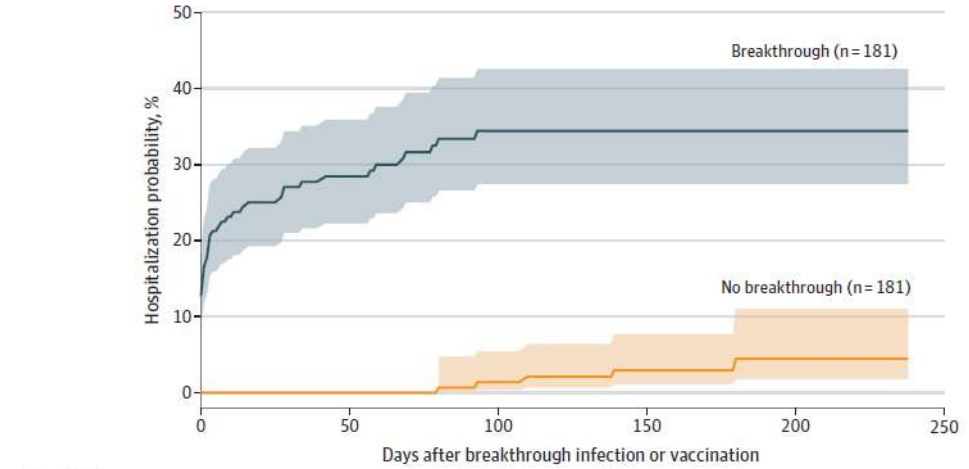
JAMA Network Open. 2021;4(11):e2137575.

Research Letter | Hematology

Risks of SARS-CoV-2 Breakthrough Infection and Hospitalization in Fully Vaccinated Patients With Multiple Myeloma

Lindsey Wang; Nathan A. Berger, MD; Rong Xu, PhD

Figure. Risk of Hospitalization for Patients With vs Without Breakthrough COVID-19 Infection



No. at risk						
Breakthrough	181	100	64	64	64	64
No breakthrough	181	140	115	62	62	62

COVID-19 in vaccinated adult patients with hematological malignancies. Preliminary results from EPICOVIDEHA

Pagano L. et al

Mortality according to type of hematological malignancy		
Acute lymphoid leukemia	0/3	0.0
Chronic lymphoid leukemia	2/28	7.1
Acute myeloid leukemia	0/5	0.0
Chronic myeloid leukemia	0/1	0.0
Myelodysplastic syndrome	2/7	28.6
Hodgkin lymphoma	1/4	25.0
Non-Hodgkin lymphoma	6/36	16.7
Myelofibrosis	1/3	33.3
Polycythemia vera	0/2	0.0
Systemic mastocytosis	1/2	50.0
Multiple myeloma	1/20	5.0
Aplastic anemia	0/2	0.0

COVID-19 vaccination: message to MM patients

- COVID-19 vaccination is effective if a full vaccination including the third dose is given.
- Protection could be reduced in patients:
  - With advanced disease
  - Undergoing certain treatments
  - With other risk factors
- Vaccination is however strongly recommended even in these cases
- Patients with MM who get the infection acquire a greater immune response if they are then vaccinated.
- Nevertheless, up to a favorable evolution of the pandemic, patients must continue to follow the rules for preventing the transmission of COVID-19 and vaccination of family members and care giver is recommended