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# Serological response to SARS-CoV-2 mRNA-LNP vaccine in patients with multiple myeloma: a negative impact of CD38+ Treg?



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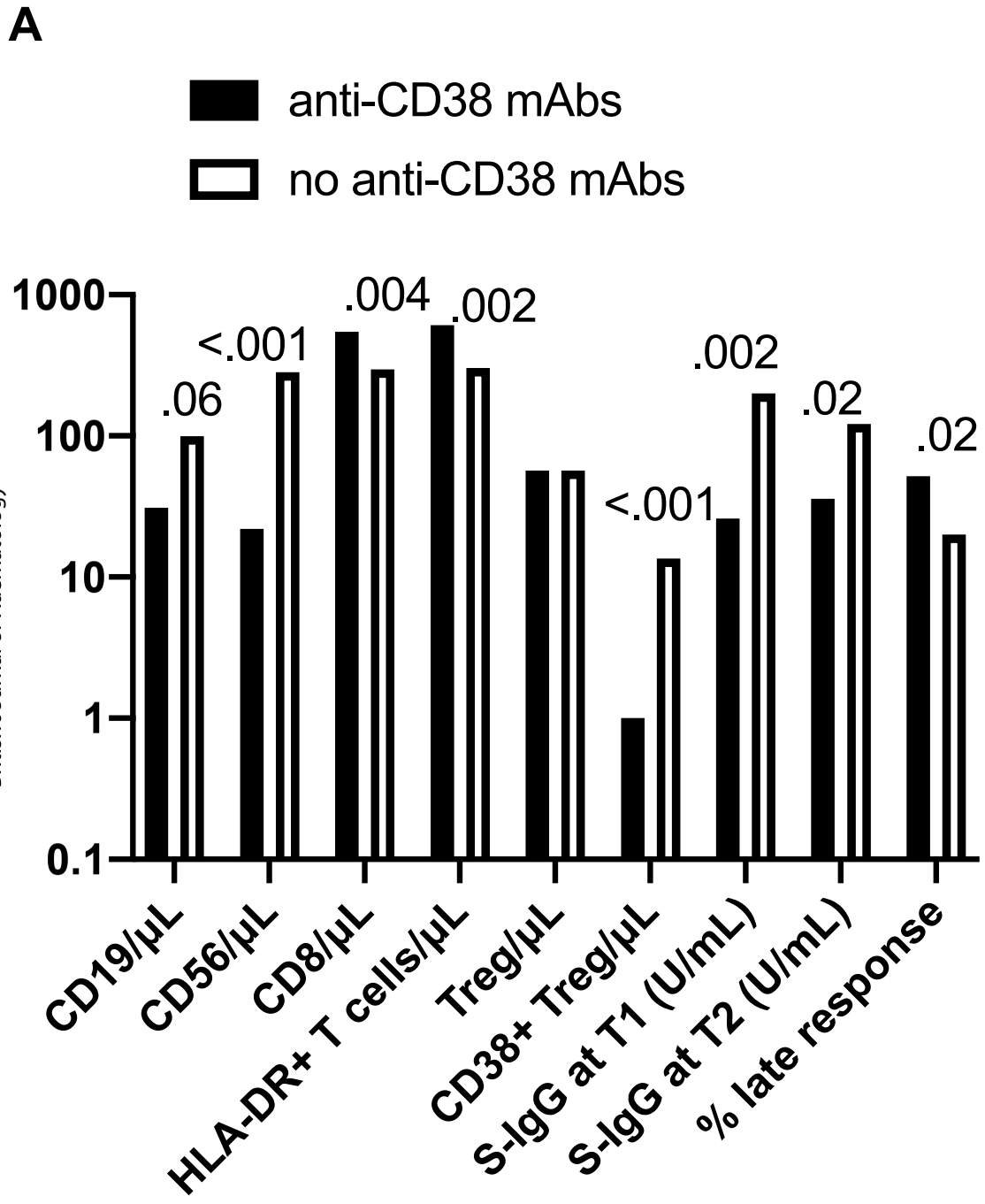
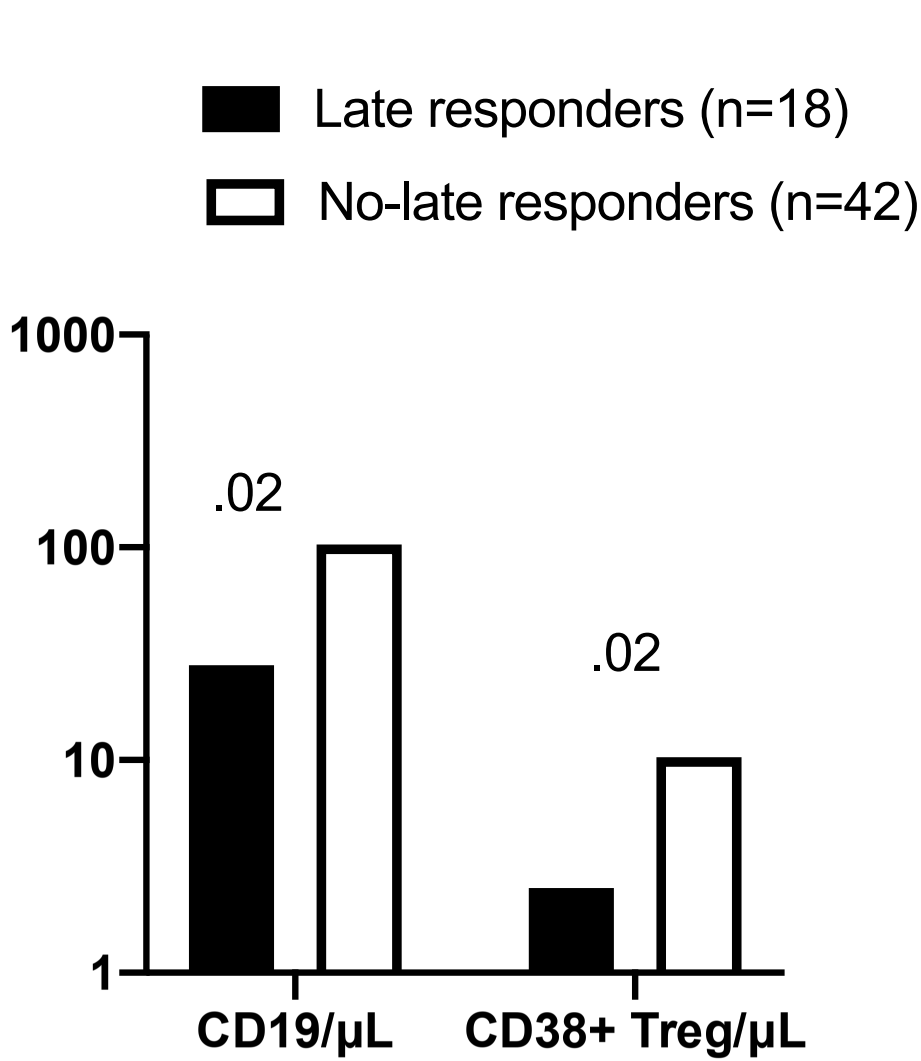

A
anti-CD38 mAbs
no anti-CD38 mAbs
1000
100
10
1
0.1
.06
<.001
.004
.002
<.001
.002
.02
.02
CD19/µL
CD56/µL
CD8/µL
HLA-DR+ T cells/µL
Treg/µL
CD38+ Treg/µL
S-IgG at T1 (U/mL)
S-IgG at T2 (U/mL)
% late response


B
Late responders (n=18)
No-late responders (n=42)
1000
100
10
1
.02
.02
CD19/µL
CD38+ Treg/µL

# Serological response to SARS-CoV-2 mRNA-LNP vaccine in patients with multiple myeloma: a negative impact of CD38$^{+}$ Treg?

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Commentary on: Terao et al. Depletion of CD38-positive regulatory T-cells by anti-CD38 monoclonal antibodies induces a durable response to SARS- CoV-2 vaccination in patients with plasma cell dyscrasia; BJHaematol 2022 volume and page to be determined.

The immunogenicity of SARS-CoV-2 spike mRNA-containing lipid nanoparticles (LNPs) vaccines (such as BNT162b2 and mRNA-1273) has been extensively studied (1). It was found that following BNT162b2 or mRNA-1273 vaccination, injected mRNA-LNPs are incorporated by dendritic cells (DC). These DC traffic to the draining lymph nodes where they present SARS-CoV-2 spike antigens and prime CD4$^{+}$ and CD8$^{+}$ T cells. Primed CD4$^{+}$ T cells then differentiate into either Th1 or T follicular helper (Tfh) spike-specific T cells. These Tfh play a pivotal role by initiating and maintaining strong germinal center reactions which eventually lead to the generation of spike-specific memory B cells and of long-lived plasma cells, resulting in the secretion of binding and neutralizing antibodies (Ab) against the spike protein. It should be noted that this germinal center formation is enhanced by LNPs which, in addition to their role of carrier, act as a strong adjuvant.

Regulatory T cells (Treg) are key regulators of immune reactions. These CD4$^{+}$ T cells are characterized by the constitutive expression of the transcription factor Foxp3 and the IL-2

receptor α chain CD25. They however have a low expression of the IL-7 receptor CD127. Previous work on the impact of Treg on vaccination showed that a subset of Treg, termed follicular regulatory T cells (Tfr) regulate Tfh cells and control unspecific growth of the germinal center response during a T cell-dependent immune reaction (2). Further, in the absence of adjuvants, transient Treg depletion favors DC maturation in the draining lymph nodes after immunization with the SARS-CoV-2 spike antigen (3). This results in the production of spike-specific $CD4^+$ and $CD8^+$ T cells producing interferon-gamma. However, there is only limited data on the impact of Treg on mRNA-LNPs vaccine immunogenicity. Indeed systems biology (i.e. multi omic) analyses did not observe an induction of Treg following BNT162b2 vaccination although higher levels of pSTAT1 and pSTAT3 in Treg were observed one day after the second vaccine administration (4). In addition, no correlations were found between baseline Treg counts and Ab response to BNT162b2 vaccination in allogeneic hematopoietic stem cell transplant recipients while positive correlations were observed with memory B cells, naive $CD4^+$ T cells and Tfh cell counts (5)(6).

In comparison to healthy controls, patients with multiple myeloma (MM) have a lower serological response to SARS-CoV-2 mRNA vaccine (7). This is particularly true in patients given BCMA-targeted therapies and in those given the anti-CD38 monoclonal Ab (mAb). CD38 is a transmembrane glycoprotein which is highly expressed on MM cells as well as on normal plasma cells (8). It is thus not unexpected that anti-CD38 mAb affect serological response to mRNA vaccines. Anti-CD38 mAbs have additional immunomodulatory effects by (1) depleting $CD38^+$ Treg cells, known to be more immunosuppressive than the $CD38^-$Treg, and (2) eliminating regulatory B- and myeloid-derived suppressor cells (8). In addition, Tfr (and particularly PD-$1^+$ Tfr) express high levels of CD38 (9), suggesting that their destruction by anti-CD38 mAb might promote germinal center formation and increase mRNA vaccine efficacy.

In this issue of the journal, Terao *et al.* report the impact of $CD38^+$ Treg depletion with anti-CD38 mAbs on serological response to two doses of anti-SARS-Cov-2 mRNA vaccine in sixty patients with plasma cell dyscrasia (10). Fifty-nine patients were given the BNT162b2 and one the mRNA-1273 vaccine. Confirming observations by other groups of investigators, patients given anti-CD38 mAbs (n=26) had lower anti-spike IgG both at 4 weeks (T1) and at 12 weeks (T2) after second vaccination (Figure 1A). Interestingly, serological responses declined between T1 and T2 in patients not receiving anti-CD38 mAbs, but they remained stable in patients on anti-CD38 mAbs. The authors then investigated whether this phenomenon could be explained by $CD38^+$ Treg depletion by anti-CD38 mAbs. As expected, patients on anti-CD38 mAbs had lower $CD38^+$ Treg counts than the other patients (1.0 versus 13.5/ µL, $P<0.001$) (Figure 1A). Interestingly, patients with $CD38^+$ Treg > 4.8/uL (n=35) had declining anti-spike IgG levels while patients with $CD38^+$ Treg counts <= 4.8/uL (n=25) maintained and (slightly) increased their anti-spike IgG levels (from 30 U/mL at T1 and 72 U/mL at T2). Finally, late responders (defined as patients whose anti-spike IgG increased from T1 to T2, n=18) had lower $CD38^+$ Treg counts as compared to non-late responders (Figure 1B). These findings are of interest since they provide indirect evidence that $CD38^+$ Treg may shut down immune response to mRNA vaccines. There are however a few limitations in the study by Terao *et al.* including the fact that FoxP3 staining was not used to define Treg (they were defined as $CD4^+CD25^+CD127^{dim}$ cells which is suboptimal) as well as the fact that neutralizing Ab as well as T-cell responses to the vaccine were not assessed. Nevertheless, the study by Terao *et al.* provides a good background to stimulate further research aimed at investigating the impact of $CD38^+$ Treg and $CD38^+$ Tfr on mRNA vaccine immunogenicity.

## References

1. Hogan MJ, Pardi N. mRNA Vaccines in the COVID-19 Pandemic and Beyond. Annu Rev Med. 2022;73:17-39.

2. Linterman MA, Pierson W, Lee SK, Kallies A, Kawamoto S, Rayner TF, et al. Foxp3+ follicular regulatory T cells control the germinal center response. Nat Med. 24 juill 2011;17(8):975-82.

3. Uraki R, Imai M, Ito M, Shime H, Odanaka M, Okuda M, et al. Foxp3+ CD4+ regulatory T cells control dendritic cells in inducing antigen-specific immunity to emerging SARS-CoV-2 antigens. PLoS Pathog. déc 2021;17(12):e1010085.

4. Arunachalam PS, Scott MKD, Hagan T, Li C, Feng Y, Wimmers F, et al. Systems vaccinology of the BNT162b2 mRNA vaccine in humans. Nature. août 2021;596(7872):410-6.

5. Canti L, Humblet-Baron S, Desombere I, Neumann J, Pannus P, Heyndrickx L, et al. Predictors of neutralizing antibody response to BNT162b2 vaccination in allogeneic hematopoietic stem cell transplant recipients. J Hematol Oncol. 24 oct 2021;14(1):174.

6. Canti L, Ariën KK, Desombere I, Humblet-Baron S, Pannus P, Heyndrickx L, et al. Antibody response against SARS-CoV-2 Delta and Omicron variants after third-dose BNT162b2 vaccination in allo-HCT recipients. Cancer cell. 2022;in press.

7. Van Oekelen O, Gleason CR, Agte S, Srivastava K, Beach KF, Aleman A, 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. 9 août 2021;39(8):1028-30.

8. van de Donk NWCJ, Richardson PG, Malavasi F. CD38 antibodies in multiple myeloma: back to the future. Blood. 4 janv 2018;131(1):13-29.

9. Sayin I, Radtke AJ, Vella LA, Jin W, Wherry EJ, Buggert M, et al. Spatial distribution and function of T follicular regulatory cells in human lymph nodes. J Exp Med. 4 juin 2018;215(6):1531-42.

10. Terao T, Naduka T, Ikeda D, Fukumoto A, Kamura Y, Kuzume A, et al. Depletion of CD38-positive regulatory T-cells by anti-CD38 monoclonal antibodies induces a durable response to SARS-CoV-2 vaccination in patients with plasma cell dyscrasia. British journal of haematology. :in press.

## Declaration of interests

FB has received travel grants from Pfizer, Celgene, Abbvie, Novartis and Sanofi as well as honoraria from Merck and Abbvie. JC has received honoraria and research funding from Jansen Oncology. SHB declares no relevant conflict of interest.

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## Legend to the figure.

**Figure 1.** (A) Blood counts at baseline and serological response to the vaccine in patients on anti-CD38 mAbs within 3 months before first vaccine versus in other patients in the study by Terao et al.. T1: 4 weeks after second vaccine; T2: 12 weeks after second vaccine. (B) CD19 and CD38+ Treg counts in late responders (defined as patients whose anti-S IgG increased from T1 to T2) versus in non-late responders in the study by Terao et al..