KYRIOS clinical trial: Tracking the immune response to SARS-CoV-2 mRNA vaccines in an open-label multicenter study in participants with relapsing multiple sclerosis treated with ofatumumab s.c.

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Disclosures

Tjalf Ziemssen has received research support, consulting fee, and honoraria for lectures from Alexion, Biogen, Celgene, Merck, Novartis, Roche, Sanofi, Teva.

Tobias Bopp has received consulting fee and honoraria for lectures from Biogen, Celgene, Merck, Novartis, Pathios Therapeutics, Roche, Sanofi Genzyme, Teva.

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Introduction

- Initial and booster vaccination with the newly developed SARS-CoV-2 mRNA vaccines efficiently protect healthy individuals against COVID-19, but little is known about the efficacy of these vaccines in patients with Multiple Sclerosis (MS) treated with anti-CD20 therapies.

- Ofatumumab is the first fully-human anti-CD20 antibody authorized by the EMA for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease. Ofatumumab is applied once monthly s.c. (20 mg) and selectively depletes B-cells, which represent one pillar of the adaptive immune response.

- With regards to the newly developed SARS-CoV-2 mRNA vaccines it could however been shown that they not only induce selective B- but also T-cell responses[1,2].

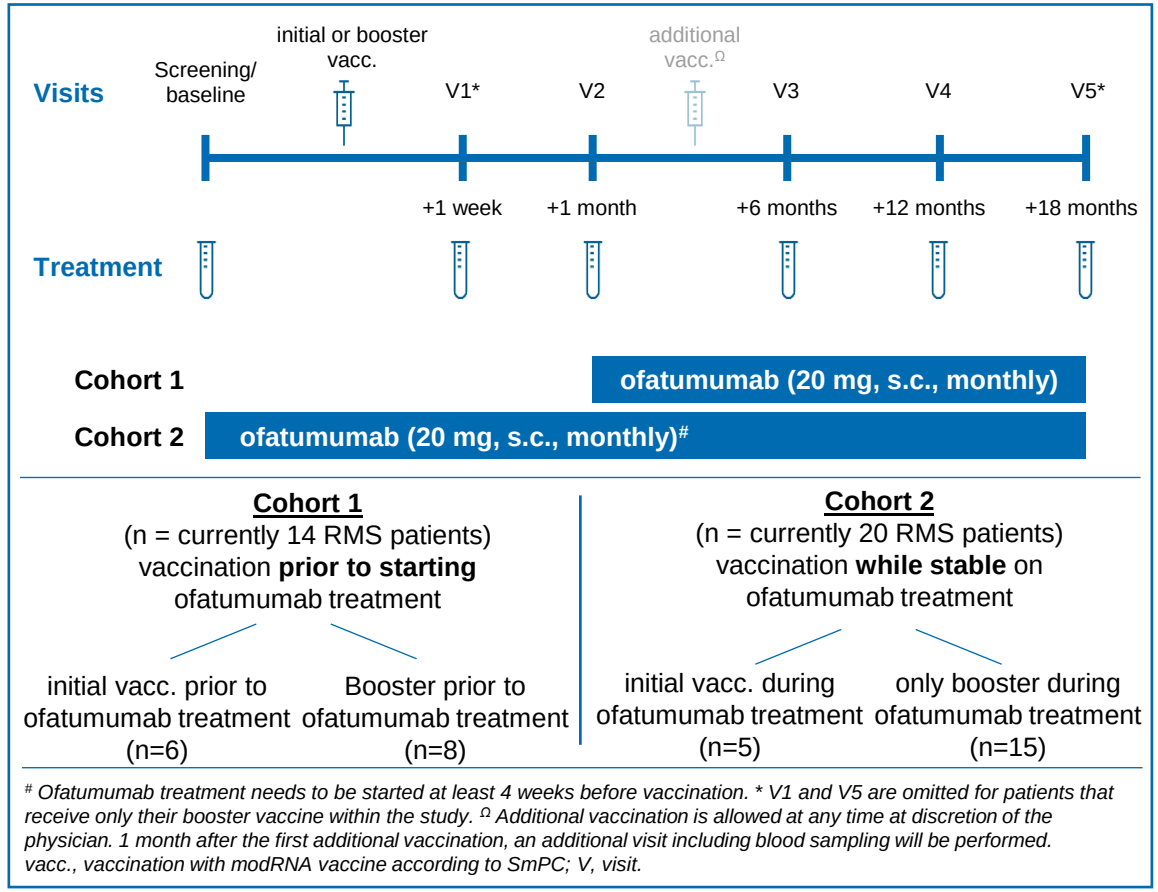
- **The aim of this study is therefore to understand the impact of ofatumumab treatment on mounting cellular and humoral immune responses after initial and booster SARS-CoV-2 mRNA vaccination.**

1. Sahin et al. (2021) Nature. 595,572–577. **2.** Jackson et al. (2020) N Engl J Med. 383:1920-1931.

Methods

- KYRIOS is a prospective, open-label, two-cohort study including 34 RMS patients at 8 sites in Germany (**Figure 1**).
  - Patients receive initial or booster SARS-CoV-2 mRNA vaccination either before (**control cohort, cohort 1**) or at least 4 weeks after starting ofatumumab treatment (**cohort 2**).
  - Immune responses after initial and booster vaccination were analyzed separately.
- Ofatumumab treatment is administered as part of the study and vaccinations as part of clinical routine according to summary of product characteristics (SmPC).
- **Neutralizing antibodies** were analyzed utilizing the cPassTMSARS-CoV-2 Neutralization Antibody Detection Kit from GenScriptUSA Inc(L00847).
- **SARS-CoV-2 specific T-cells** were detected with the CoV-iSpot Interferon-γ + Interleukin-2 (ELSP 7010 strip format) from GenID®GmbH. Each ELISpot assay was performed with $2x10^6$ PBMCs (peripheral blood mononuclear cells).

Figure 1: Study design



*# Ofatumumab treatment needs to be started at least 4 weeks before vaccination. * V1 and V5 are omitted for patients that receive only their booster vaccine within the study. Ω Additional vaccination is allowed at any time at discretion of the physician. 1 month after the first additional vaccination, an additional visit including blood sampling will be performed. vacc., vaccination with modRNA vaccine according to SmPC; V, visit.*

RMS = Relapsing Multiple Sclerosis

Demographics and baseline information

- Patient characteristics at the time of screening are shown in **Table 1**.
  - At data cut-off, 33 patients were enrolled in the study with a mean age of 41.6 years and a disease history of 6.7 years.
  - 50% of patients in cohort 1 and 26% in cohort 2 were treatment naive.
- > 90% of patients received BioNTech/Pfizer SARS-CoV-2 mRNA vaccines with an average of 4.8 weeks between 1st and 2nd dose.
- Booster vaccines were administered on average 6.1 months after 2nd dose and mostly (90%) with the same vaccine as in the initial vaccination cycle.
- B-cell depletion was verified in subjects of cohort 2 before vaccination.

Table 1: Patient characteristics

Variable*	Cohort 1 – vaccination prior to treatment	Cohort 2 – vaccination during stable treatment
N	14	19
Age, years	40.84 [23; 79]	42.08 [21; 61]
Sex, female, n (%)	10 (41.7)	11 (61.1)
Time since diagnosis, years	7.5 [0; 23]	6.1 [0; 19]
Prior treatments before ofatumumab		
Naive, N (%)	7 (50)	5 (26.3)
One, N (%)	2 (14.3)	4 (21.1)
Two, N (%)	0 (0)	5 (26.3)
More than two, N (%)	5 (35.7)	5 (26.3)
Vaccination, n (%)		
1st (BioNTech | Moderna)	13 (92.9) | 1 (7.1)	18 (94.7) | 1 (5.3)
2nd (BioNTech | Moderna)	13 (92.9) | 1 (7.1)	18 (94.7) | 1 (5.3)
Booster (BioNTech | Moderna)	7 (87.5) | 1 (12.5)	11 (84.6) | 2 (15.4)
Vaccination time interval (days)		
1st to 2nd vaccination	30.8 [21; 42]	35.7 [21; 56]
2nd vaccination to Booster	182 [160; 216]	187 [129;295]
CD19+/CD20+ cells at baseline (cells/µl)	215.7 [7; 535]	0.1 [0;1]

* if not indicated otherwise, data are presented as mean [min; max]; #depending on subcohort, vaccine refers to either initial vaccination or booster vaccination

RMS = Relapsing Multiple Sclerosis

Results
after initial vaccination cycle

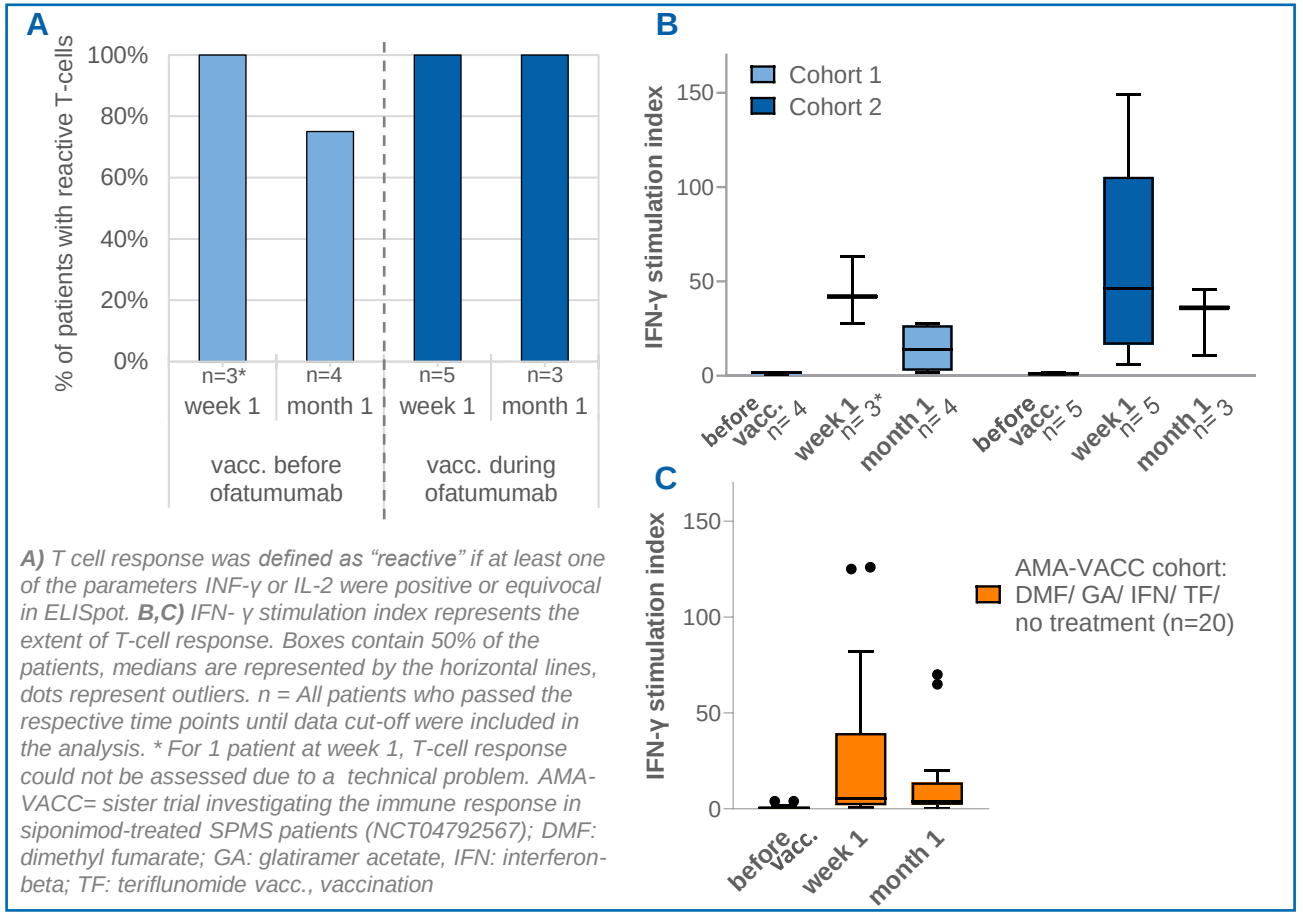
SARS-CoV-2 specific T-cell response

- T-cell response was measured by secretion of IFN-γ and/or IL-2 after stimulation of peripheral blood mononuclear cells (PBMCs) with SARS-CoV-2 peptide mix (ELISpot), which is a time sensitive and technically challenging method.
- In total, n=5 and n=6 patients received their initial vaccinations in cohort 1 and 2, respectively. As this is an interim analysis, data is still incomplete.
- All patients (5/5) receiving initial vaccination during stable ofatumumab treatment developed SARS-CoV-2 reactive T-cells as soon as 1 week after full vaccination (**Figure 2A**).
- Extent of T-cell response in these patients peaked at 1 week after full vaccination and was comparable to control cohort (**Figure 2B**). T-cell response was also comparable to patients receiving DMF, GA, IFN, TF or no treatment assessed by the same method in the AMA-VACC trial[3] (NCT04792567, **Figure 2C**).

DMF= dimethyl fumarate; GA= glatiramer acetate, IFN= interferon-beta; IFN- γ = Interferon gamma, TF= teriflunomide, vacc = vaccination

3. Ziemssen et al., EAN 2022, OPR-133

Figure 2: SARS-CoV-2 T-cell reactivity (IFN-γ and/or IL-2)



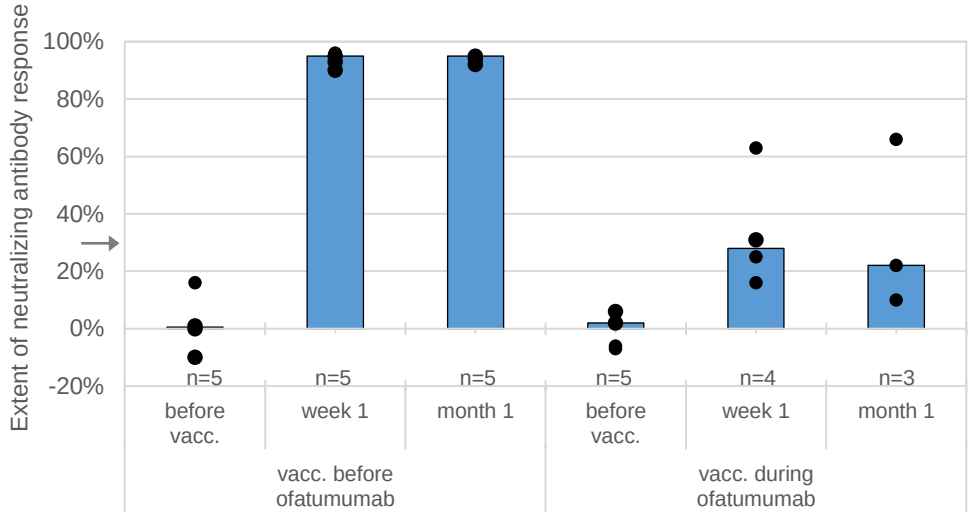
*A) T cell response was defined as "reactive" if at least one of the parameters INF-γ or IL-2 were positive or equivocal in ELISpot. B,C) IFN- γ stimulation index represents the extent of T-cell response. Boxes contain 50% of the patients, medians are represented by the horizontal lines, dots represent outliers. n = All patients who passed the respective time points until data cut-off were included in the analysis. * For 1 patient at week 1, T-cell response could not be assessed due to a technical problem. AMA-VACC= sister trial investigating the immune response in siponimod-treated SPMS patients (NCT04792567); DMF: dimethyl fumarate; GA: glatiramer acetate, IFN: interferon-beta; TF: teriflunomide vacc., vaccination*

Results
after initial vaccination cycle

Development of SARS-CoV-2 neutralizing antibodies

- Neutralizing antibodies (NAb) represent only **a subset of all specific antibodies** and are considered a **more stringent** correlate of protective immunity. Total anti-SARS-CoV-2 IgGs were not measured here but might further contribute to immunity.
- All patients (4/4) receiving their initial vaccination during stable ofatumumab treatment had an increase in NAb (**Figure 3**).
- 50% of ofatumumab patients exceeded the assay-specific cut-off for seropositivity one week after the initial vaccination cycle.

Figure 3: Development of neutralizing antibodies



Extend of neutralizing antibody response indicats the proportion of inhibited in vitro binding of purified Receptor Binding Domain (RBD) of SARS-CoV-2 spike protein and ACE2 receptor by patient serum. Bars represent medians; all patients with available data were included in the analysis and individual values are represented by dots. Arrow indicates the the assay-specific cut-off for seropositivity of 30%. vacc., initial vaccination

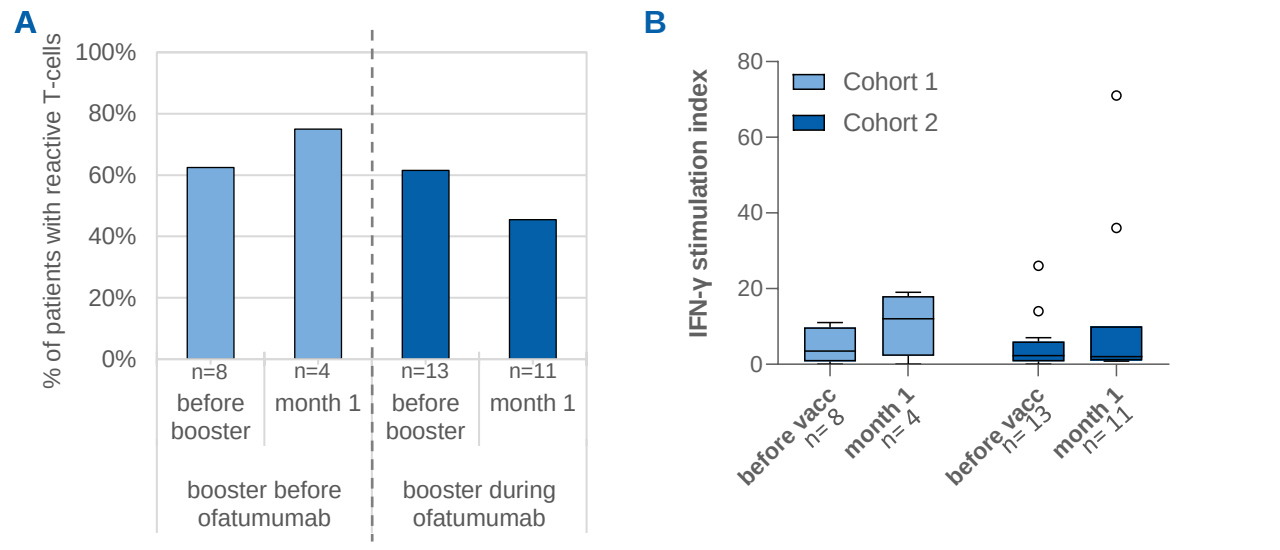
Nab = Neutralizing antibodies, RBD = receptor bindng domain vacc = vaccination

Results
after booster vaccination

SARS-CoV-2 specific T-cell response after booster

- In total, 8 and 15 patients will receive their booster vaccination in cohort 1 and 2, respectively. With this being an interim analysis, data is still incomplete.
- T-cell response was more heterogenous than after initial vaccination but comparable between cohorts (**Figure 4A**).
- Across both cohorts, most patients without T-cell response after booster (5/7) were older than 50 years.
- For both cohorts, extent of T-cell response increased after booster (**Figure 4B**).
- Hypothesis: based on observations after initial vaccination, one month after booster vaccination might be too late to detect T-cell response in some patients via ELISpot assay

Figure 4: SARS-CoV-2 T-cell reactivity (IFN-γ and/or IL-2)



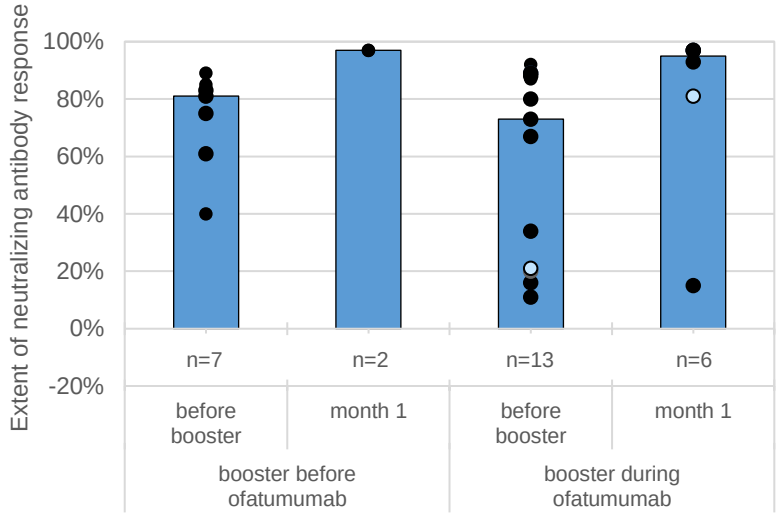
A) T-cell response measured by secretion of IFN-γ and/or IL-2 (ELIspot) after stimulation of isolated PBMCs with SARS-CoV-2 peptide mix. T cell response was defined as present if at least one of the parameters INF-γ or IL-2 were positive or equivocal. n = All patients that passed the respective time points were included in the analysis. B) IFN- γ stimulation index represents the extent of T-cell response. Boxes contain 50% of the patients, medians are represented by the horizontal lines and outliers are represented as circles. vacc., vaccination

Results
after booster vaccination

Development of SARS-CoV-2 neutralizing antibodies after booster vaccination

- All antibody samples collected until 4 weeks before data cut-off were analyzed.
- 5/6 patients boostered during stable ofatumumab treatment showed an increase in NAb until data cut-off (**Figure 5**).
- Neutralizing antibody response in ofatumumab treated patients after booster increased to a comparable extend as in control group.
- One patient who was seronegative before booster seroconverted during stable ofatumumab treatment (light blue dot).

Figure 5: Development of neutralizing antibodies



Extend of neutralizing antibody response indicats the proportion of inhibited in vitro binding of purified Receptor Binding Domain (RBD) of SARS-CoV-2 spike protein and ACE2 receptor by patient serum. Bars represent medians; all patients with available data were included in the analysis and individual values are represented by dots. Light blue dot represents patient who seroconverted after booster during stable ofatumumab treatment. Arrow indicates the the assay-specific cut-off for seropositivity of 30%. vacc., initial vaccination

NAb = Neutralizing antibodies, RBD = receptor bindng domain vacc = vaccination

Results

Safety

- One MS relapse occurred during the study (patient recovered fully, relapse occurred before 1st vaccination in a patient in cohort 2)
- Until data cut-off, two patients developed COVID-19 infections during the study:
  - One patient in cohort 1 (initial vaccination prior to ofatumumab treatment): 6 days after 2nd vaccination, CTCAE moderate, no MS therapy at time of infection, full recovery (duration of infection: 9 days)
  - One patient in cohort 2 (initial vaccination during ofatumumab treatment): 27 days after 2nd vaccination, CTCAE moderate, no interruption of ofatumumab treatment, infection was ongoing at time of data cut-off but patient has by now fully recovered (duration of infection: 13 days)

CTCAE = Common Terminology Criteria for Adverse Events

Conclusions

- **Immune response could be detected in all patients (5/5) vaccinated during continuous ofatumumab as soon as one week after initial vaccination cycle.**
  - Ofatumumab treatment did not affect the development of SARS-CoV-2 specific T-cell response.
  - All patients showed an increase in neutralizing antibodies. Although the extent was lower versus control group, 50% exceeded the cut-off value for seropositivity.
  - These results are in line with previously reported low rate of COVID-19 infections in vaccinated patients treated with ofatumumab[4]
- **Patients boostered before and during ofatumumab treatment showed similar immune responses.**
  - In 6/7 ofatumumab patients, neutralizing antibodies increased to a comparable extent as in control cohort
  - For one patient, seroconversion during continuous ofatumumab treatment was observed after booster
  - T-cell response was heterogenous but comparable between cohorts. However, T-cell data is still incomplete and needs to be interpreted with caution.
- Despite limited sample size, population heterogeneity and pending longitudinal data, we can conclude that both cellular and humoral response need to be considered for interpretation of vaccine efficacy.
- The next interim analysis will include longidutinal data as well as total and neutralizing anti-SARS-CoV-2 antibody titers.

4. Cross et al. (2022) Neurology and Therapy