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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Background

- 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].

Objective

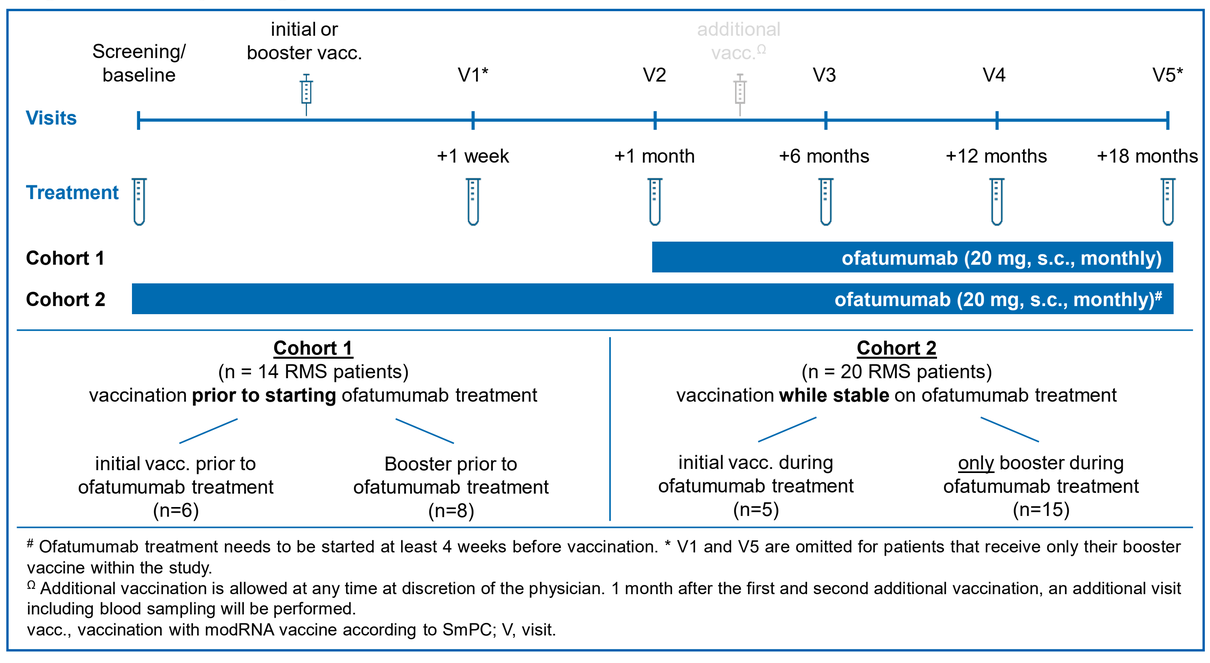
- The aim of this study is therefore to understand the **impact of ofatumumab treatment** on mounting **cellular and humoral immune responses** after initial and booster **SARS-CoV-2 mRNA vaccination**.

Methods

Study design

- KYRIOS is a prospective, open-label, two-cohort study including 34 RMS patients at 8 sites in Germany (**Figure 1**).
- Preliminary results of the interim analysis are demonstrated. All patients with available data as of June 30th 2022 cut-off date were included in the analysis.
  - 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.

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 and second additional vaccination, an additional visit including blood sampling will be performed.
vacc., vaccination with modRNA vaccine according to SmPC; V, visit.

- 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 (Nab) were analyzed utilizing the cPassTMSARS-CoV-2 Neutralization Antibody Detection Kit from GenScriptUSA Inc(L00847). Total anti-spike antibody titers were measured using Elecsys Anti-SARS-CoV-2 S immuno-assay from Roche.
- 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 $2x10^5$ PBMCs (peripheral blood mononuclear cells).

Results

Demographics and baseline information

- Patient characteristics at the time of screening are shown in **Table 1**.
  - In total, 34 patients were enrolled in the study with a mean age of 41.6 years and a disease history of 6.5 years.
  - 50% of patients in cohort 1 and 40% 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 5.7 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.

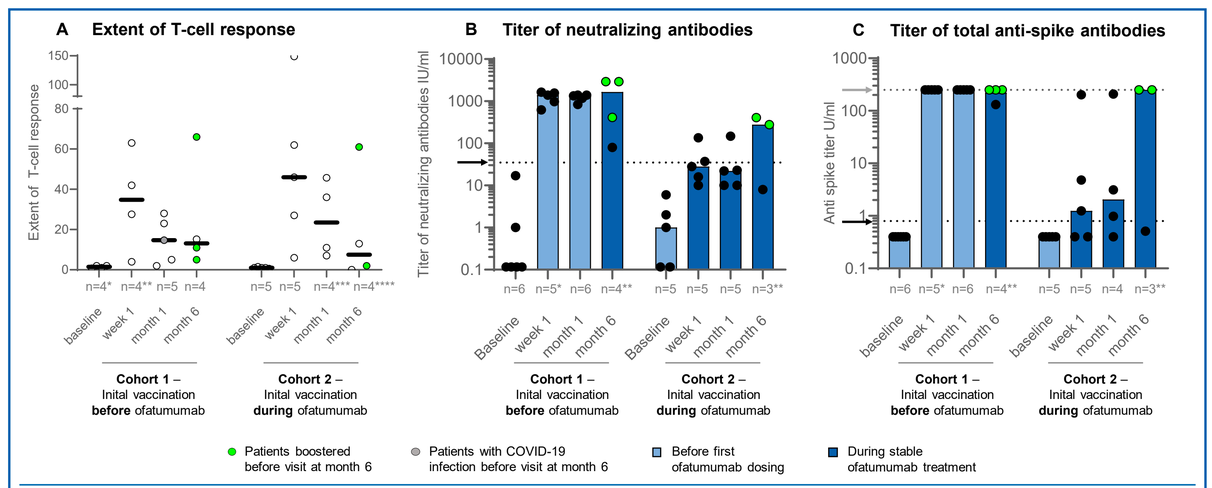
Table 1. Patient characteristics

Variable [min; max]	Cohort 1 – vaccination prior to treatment	Cohort 2 – vaccination during stable treatment
N	14	20
Age, years	40.9 [23; 79]	42.2 [21; 61]
Sex, female, n (%)	10 (71.4)	13 (65.0)
Time since first MS diagnosis, years	7.5 [0; 23]	5.8 [0; 19]
Prior treatments before ofatumumab		
Naive, n (%)	7 (50.0)	8 (40.0)
One, n (%)	2 (14.3)	5 (25.0)
Two, n (%)	0 (0.0)	6 (30.0)
More than two, n (%)	5 (35.7)	1 (5.0)
Vaccination, n (%)		
1st (BioNTech | Moderna)	13 (92.9) | 1 (7.1)	19 (95.0) | 1 (5.0)
2nd (BioNTech | Moderna)	13 (92.9) | 1 (7.1)	19 (95.0) | 1 (5.0)
Booster (BioNTech | Moderna)	7 (50.0) | 1 (7.1)	13 (65.0) | 2 (10.0)

SARS-CoV-2 specific T-cell response and development of neutralizing antibodies after initial vaccination cycle

- 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. Extent of T-cell response peaked at 1 week after full vaccination and was comparable between cohorts (**Figure 2A**).
- All patients (5/5) receiving their initial vaccination during stable ofatumumab treatment had an increase in NAb (**Figure 2B**). 40% of ofatumumab patients were seropositive for NAb (**Figure 2B**) and 60% for anti-spike antibodies (**Figure 2C**) one week after the initial vaccination cycle.
- First trend shows that booster vaccination even when applied approx. 6 months after initial vaccination cycle distinctly increased the level of neutralizing and anti-spike antibodies in ofatumumab-treated patients (green dots).

Figure 2. SARS-CoV-2 T-cell reactivity (IFN-γ) (A) and development of neutralizing and anti-spike antibodies (B, C) after initial vaccination cycle

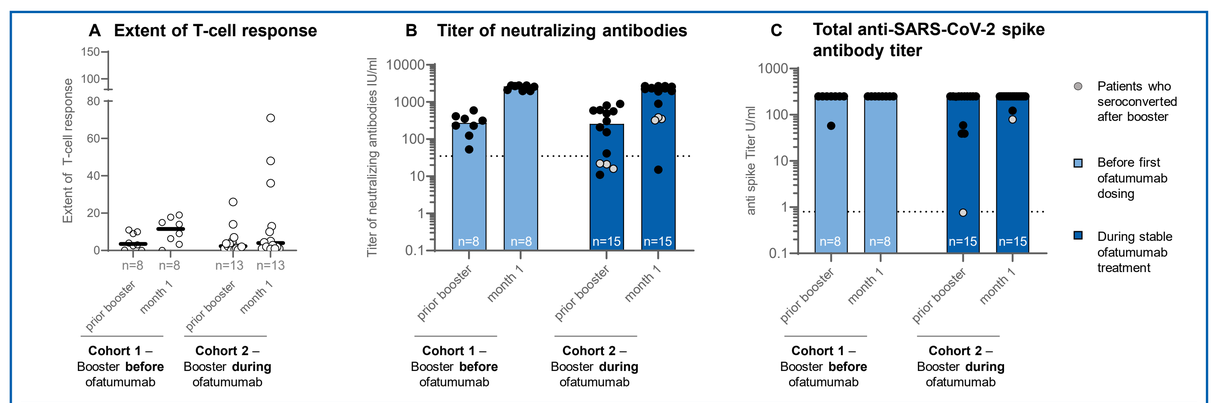


(A) Extent of T-cell response represents the IFN-γ stimulation index. Each dot represents one patient, medians are indicated by horizontal lines. All patients who passed the respective time points until data cut-off were included in the analysis. *For 1 patient at baseline, T-cell response could not be assessed due to technical problems. **One patient in cohort 1 discontinued the study and skipped the visit at week 1. ***For one patient at month 1, visit could not be performed due to a COVID-19 infection. ****For one patients at month 6, data was still missing at data cut-off.
(B+C) All patients with available data were included in the analysis and individual values are represented by dots. Bars show median values, black arrows indicate assay-specific cut-off for seropositivity, grey arrow the maximal value of quantification range. *n=1 patient discontinued the study and skipped visit 1. **For multiple patients, data was still missing at cut-off.

SARS-CoV-2 specific T-cell response and development of neutralizing antibodies after booster vaccination

- T-cell response was comparable between cohorts (**Figure 3A**). 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.
- Neutralizing antibody response in ofatumumab treated patients after booster increased to a comparable level as in control group (**Figure 3B+C**). 3/4 patients who were seronegative for NAb before booster seroconverted during stable ofatumumab treatment (grey dots). All patients boostered during stable ofatumumab treatment also showed an increase in anti-spike antibodies 1 month after booster including one previously seronegative patient.

Figure 3. SARS-CoV-2 T-cell reactivity (IFN-γ) (A) and development of neutralizing and anti-spike antibodies (B, C) after booster vaccination



(A) Extent of T-cell response represents the IFN-γ stimulation index. Each dot represents one patient, medians are indicated by horizontal lines. All patients received their initial vaccination cycle before starting ofatumumab treatment.
(B+C) All patients with available data were included in the analysis and individual values are represented by dots. Bars show median values, dotted line indicates the the assay-specific cut-off for seropositivity. All patients received their initial vaccination cycle before starting ofatumumab treatment.

Safety

- Three MS relapses occurred during the study (all patients recovered fully; two relapses in cohort 1 and one relapse in cohort 2).
- Until data cut-off, ten patients developed COVID-19 infections during the study after full course of vaccination (**Table 2**).

Table 2. Details on COVID-19 infections

Variable [min; max]	Cohort 1	Cohort 2
Number of COVID-19 infections	2	8
Mean duration of infections (days)	9 [8; 10]	13.6 [9; 25]
CTCAE grade (mild | medium)	1 | 1	1 | 7
Fully recovered	2	8
Temporary treatment interruption	0	2

Conclusions

- **T-cell response** was not affected by ofatumumab treatment after initial and booster vaccination.
- **Neutralizing antibody response after initial vaccination** was present but reduced in ofatumumab patients. First data show that booster vaccination further increased neutralizing antibody titers in ofatumumab patients suggesting the **development of immune memory cells** after their initial vaccination.
- **Neutralizing antibody response after booster** was similar in patients boostered before and during stable ofatumumab treatment. After booster, 3/4 previously seronegative patients seroconverted during continuous ofatumumab treatment.
- Interim results suggest that **booster vaccines** increase immune response in vast majority of ofatumumab treated patients independently of their treatment status during initial vaccination.
- Mounting of immune response as assessed in this study is in line with clinical data from ALITHIOS[3] regarding **severity and duration of COVID-19 infections** in ofatumumab treated patients: all infections were CTCAE grate mild or moderate with unobtrusive course of disease.

References

1. Sahin et al. Nature 2021; 595:572–577. 2. Jackson et al. N Engl J Med 2020; 383:1920-1931. 3. Cross et al. Neurology & Therapy 2022.

Disclosures

Tjalf Ziemssen has received research support, consulting fee, and honoraria for lectures from Alexion, Biogen, Celgene, Merck, Novartis, Roche, Sanofi, Teva. **Eugen Schlegel** has received research support, consulting fee and honoraria for lectures from Biogen, Lilly, Merck and Novartis. **Tobias Bopp** has received consulting fee and honoraria for lectures from Biogen, Celgene, Merck, Novartis, Pathios Therapeutics, Roche, Sanofi Genzyme, Teva. **Benjamin Ettle** and **Marie Groth** are employees of the Novartis Pharma GmbH, Nuremberg, Germany.

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