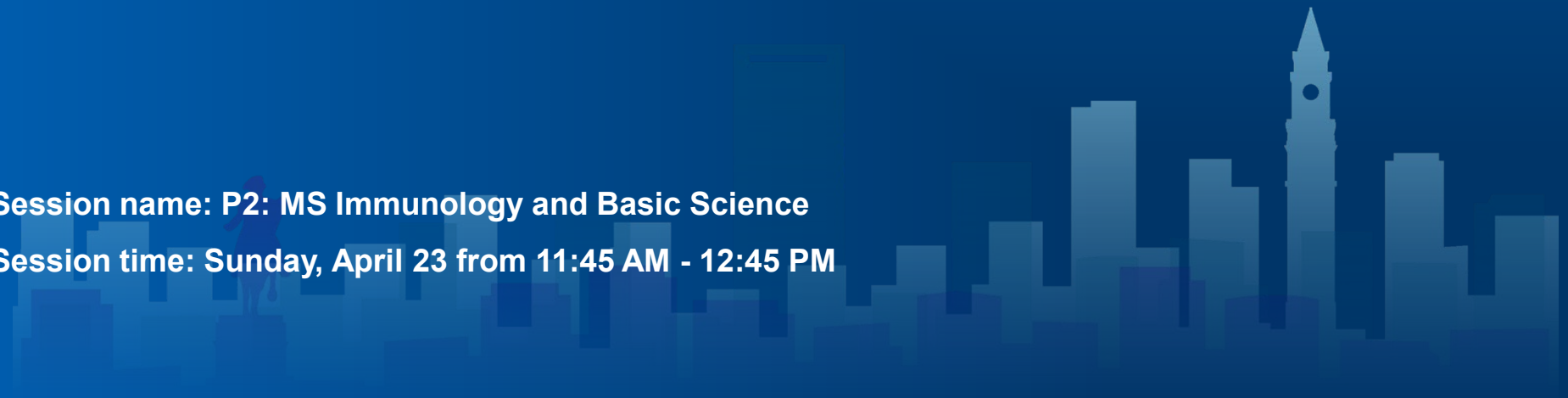
Tracking the immune response to SARS-CoV-2 mRNA booster vaccination in an open-label multicenter study in participants with relapsing multiple sclerosis treated with ofatumumab s.c. (KYRIOS clinical trial)

Tjalf Ziemssen[1], Marie Groth[2], Veronika E. Winkelmann[2], Tobias Bopp[3]

[1]Center of Clinical Neuroscience, Dresden University of Technology, Dresden, Germany; [2]Novartis Pharma GmbH, Nuremberg, Germany; [3]Institute for Immunology, University Medical Center, Mainz, Germany



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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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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].

1. Sahin et al. Nature 2021; 595:572. 2. Jackson et al. N Engl J Med 2020; 383:1920.

Objective

This study aims at understanding the impact of ofatumumab treatment on the development of cellular and humoral immune responses to initial and booster SARS-CoV-2 mRNA vaccines.

Methods

- KYRIOS is a prospective, open-label, two-cohort study including 34 RMS patients at 8 sites in Germany (**Figure 1**).
  - **Cohort 1:** patients receive SARS-CoV-2 mRNA booster vaccination before initiation of ofatumumab treatment
  - **Cohort 2:** patients receive SARS-CoV-2 mRNA booster vaccination during stable ofatumumab treatment (for at least 4 weeks)
  - **Cohort 3**: patients receive SRAS-CoV-2 mRNA booster vaccination during first-line treatment or no treatment as part of the AMA-VACC study
- 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). Total **anti-spike antibody titers** were measured using Elecsys Anti-SARS-CoV-2 S immunoassay 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).

RMS = Relapsing Multiple Sclerosis

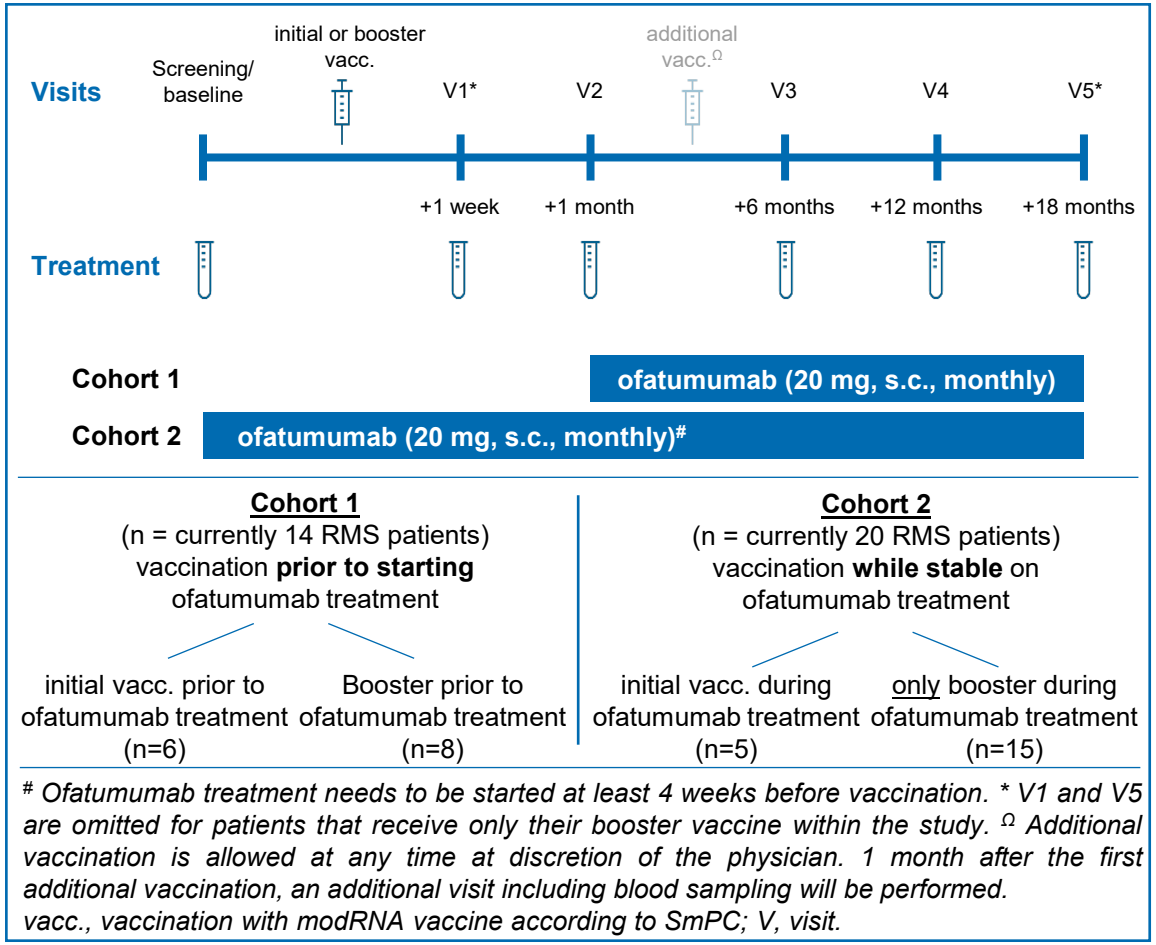


Figure 1: Study design

Patient characteristics & Vaccination characteristics

- Patient characteristics (at screening) and vaccination characteristics are depicted in **Table 1**.
- In total, 23 patients were enrolled in the KYRIOS study for their booster vaccination and 20 patients from the AMA-VACC study were selected as control group
- 95% of patients received BioNTech/Pfizer SARS-CoV-2 mRNA vaccines as first and second vaccination and 76% as booster vaccination with an average of 5.4 weeks between 1st and 2nd dose and 5.93 months between 2nd dose and booster.
- B-cell depletion was verified in subjects of cohort 2 before vaccination.

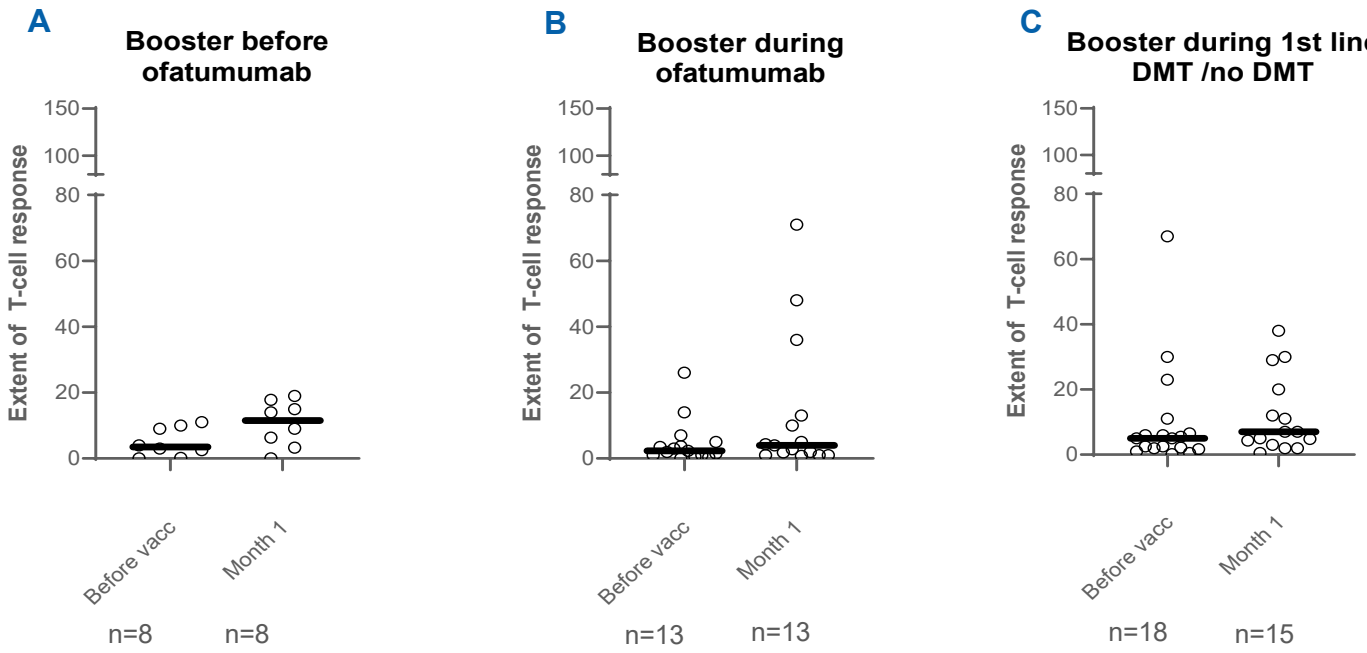
Variable°	Cohort 1 – Booster vaccination prior to ofatumumab treatment	Cohort 2 – Booster vaccination during ofatumumab treatment	Cohort 3 – 1st line DMT / no DMT
N	8	15	20[a]
Age, years	47.1 (14.1)	45.5 (12.4)	48.6 (12.9)
Sex, female, n (%)	5 (62.5)	9 (60.0)	16 (80.0)
Time since first MS diagnosis, yr	11.1 (8.7)	7.2 (7.7)	13.99 (10.43)
Number of prior DMTs	2.0 (2.1)	1.3 (1.2)	1.6 (0.7)
Vaccination, n (%)			
1st (BioNTech | Moderna)	8 (100.0) | 0 (0.0)	14 (93.3) | 1 (6.7)	19 (95.0) | 1 (5.0)
2nd (BioNTech | Moderna)	8 (100.0) | 0 (0.0)	14 (93.3) | 1 (6.7)	19 (95.0) | 1 (5.0)
Booster (BioNTech | Moderna)*	7 (87.5) | 1 (7.1)	13 (65.0) | 2 (10.0)	11 (61.1) | 7 (38.9)
Vaccination time interval			
1st to 2nd vaccination (weeks/days)	5.6 (0.7) weeks	5.6 (1.4) weeks	36.8 (9.0) days
2nd vaccination to booster (weeks/months)	26.0 (2.3) weeks	26.2 (5.9) weeks	5.82 (0.4) months

° If not indicated otherwise, data are presented as mean (SD).
a: 18 of 20 patients in the AMA-VACC study had a booster vaccination
DMT: Disease-modifying treatment; DMF: dimethyl fumarate; GA: glatiramer acetate, IFN: interferon-beta; TF: teriflunomide.

Table 1: Patient characteristics (at screening) and vaccination characteristics

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

- T-cell response was more heterogenous than after initial vaccination but comparable between cohorts (**Figure 4**).
- 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.[3]



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.

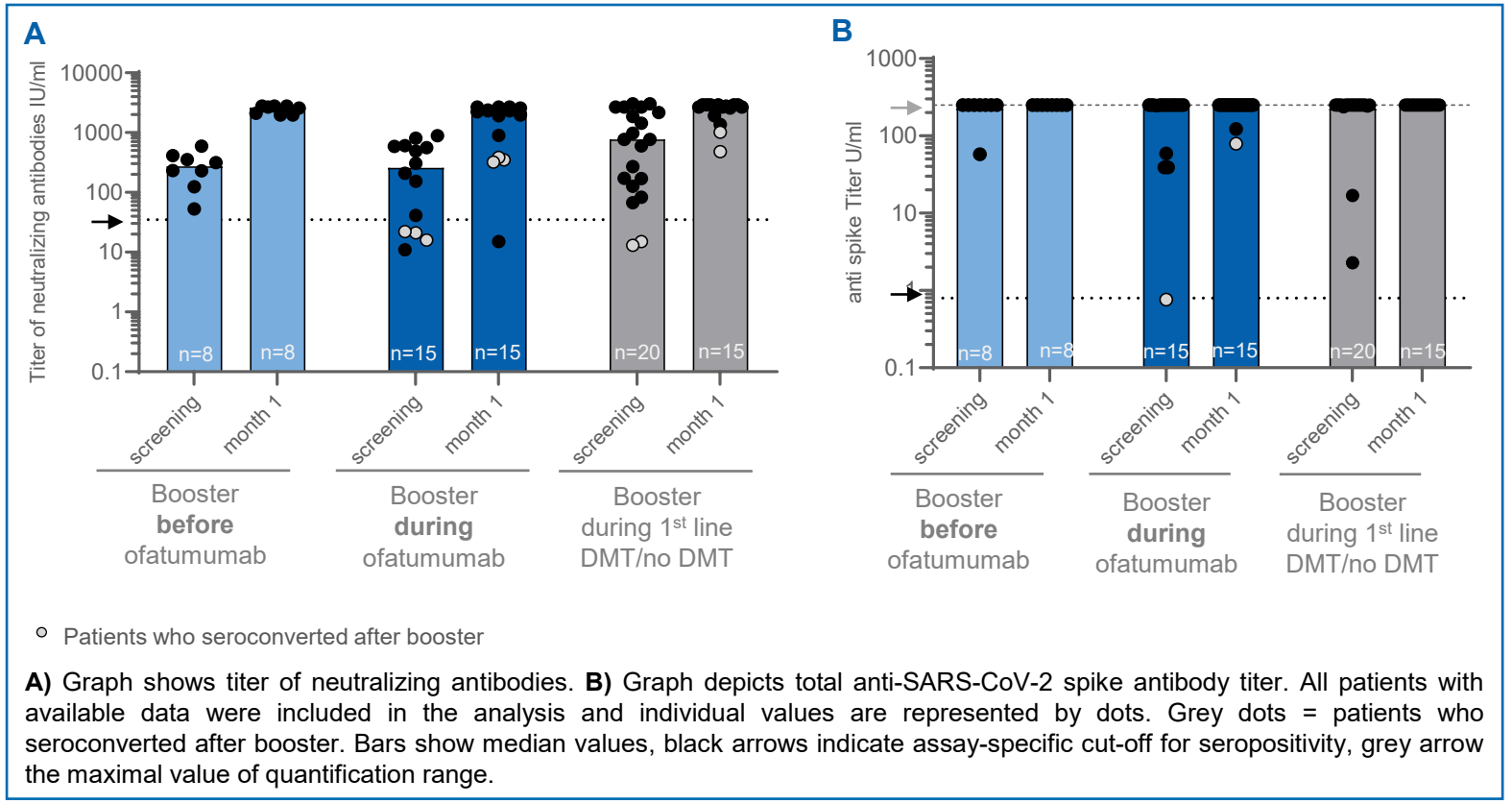
Figure 4: SARS-CoV-2 T-cell reactivity (IFN-γ and/or IL-2)

3. Ziemsen et al. Vaccines 2022; 10:1267.

Results

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

- 14/15 patients boostered during stable ofatumumab treatment showed an increase in NAb one month after booster (**Figure 5A**).
- Neutralizing antibody response in ofatumumab treated patients after booster increased to a comparable level as in control group.
- 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 5B**, grey dot)



A) Graph shows titer of neutralizing antibodies. **B)** Graph depicts total anti-SARS-CoV-2 spike antibody titer. All patients with available data were included in the analysis and individual values are represented by dots. Grey dots = patients who seroconverted after booster. Bars show median values, black arrows indicate assay-specific cut-off for seropositivity, grey arrow the maximal value of quantification range.

Figure 5: Development of neutralizing and anti-Spike antibodies

Results

- **Safety**

- Three MS relapses occurred during the study (all patients recovered fully; 2 relapses in cohort 1 and one relapse in cohort 2)

- Until data cut-off, 10 patients developed COVID-19 infections during the study:
  - 2 patients in cohort 1, 8 patients in cohort 2
  - All infections were CTCAE grade mild or moderate (level 1 and 2 on a 5-level scale)
  - Median duration of infections in cohort 1 was 8 (7-9) days and 11.5 (8-24) days in cohort 2

CTCAE = Common Terminology Criteria for Adverse Events

Conclusions

- **T-cell response was not affected by ofatumumab treatment after booster vaccination and was comparable between cohorts**
- **Neutralizing antibody response <u>after booster</u> was comparable in patients boostered before and during stable ofatumumab treatment**
  - Neutralizing antibodies in boostered ofatumumab treated patients increased to a comparable level as in control cohort
  - 3/4 patients who were seronegative for NAb before booster seroconverted during stable ofatumumab treatment

→ Mounting of immune response as assessed in this study is in line with clinical data from ALITHIOS regarding severity and duration of COVID-19 infections in ofatumumab treated patients: all infections were CTCAE grate mild or moderate with similar duration as in total population[4]

4. Cross et al. 2022; Neurol Ther; 2:741.