Cellular and humoral responses to fourth SARS-CoV-2 vaccination in a real life cohort of patients with cancer

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To the Editor,

Patients with cancer are at increased risk of adverse outcomes when infected with SARS-CoV-2 and show an impeded humoral and cellular immune response to vaccination (1). A fourth vaccination increased the humoral immunity against SARS-CoV-2 including Omicron sublineages better than Tixagevimab and Cilgavimab (2). However, data on effects of a fourth SARS-CoV-2 vaccination on cellular immunity, particularly in relation to antibody responses, are scarce (3).

Methods : To analyze specific cellular immunity after fourth immunization, SARS-CoV-2 specific $CD4^+$ / $CD8^+$ T-cell responses were prospectively measured in 7 patients with histologically confirmed neoplastic disease before and at the next clinical visit after fourth vaccination against the SARS-CoV-2 spike protein (S) and the receptor binding domain (RBD). Moreover, IgG against S and RBD of Omicron (BA.4) and Hu-1, respectively were assessed. A >1.1-fold increase of antigen-specific proliferated cells and antibody levels compared to baseline was defined as a vaccine response. Assays were performed as described previously (4). This study was approved by the Ethics Committee of the Medical University of Vienna (vote 1427/2022) and performed according to the Declaration of Helsinki and its amendments. Informed consent was obtained from all included participants. Descriptive statistical analysis was performed using GraphPad Prism, Version 9.4.1 (San Diego, California, USA).

Results : Six patients with solid tumors and one immunocompetent patient with CNS lymphoma (median age [range] 64 years [45-78], 7 men) were prospectively included and received a fourth vaccination (one mRNA-1273 and six BNT162b2). Of these patients, 6 patients were undergoing active anti-neoplastic therapy. The baseline blood sampling was performed in median 7 months (range 5-9 months) after the third vaccine dose, while the follow-up blood sampling was done in median 21 days (range: 19-30 days) after the fourth vaccination **(Table 1)** .

Overall, clear signs of response on either humoral, cellular, or combined humoral and cellular levels were observed in 6/7 patients. However, a striking intra- and interpatient heterogeneity of immune response patterns was evident (**Figure 1**). Only 2/7 patients (patients 4 and 6) responded with combined increases in S and RBD specific $CD4^+$ and $CD8^+$ T-cell proliferation. All other patients showed inconsistent increases in T-cell activity with low vaccination responses in at least one T-cell subpopulation. Additionally, humoral response did not consistently coincide with cellular vaccine responses: patients 4 and 6, who had no or only a mild (e.g. IgG against S 0.97-fold change and 2.23-fold change, respectively) increase in antibody levels had a pronounced cellular vaccine response (e.g. CD4 against S 4-fold change and 134-fold change, respectively). Interestingly, patient 5 increased antibody levels against S without corresponding $CD4^+$ responses. Moreover,

patients with distinct antibody increases only showed mediocre vaccine responses on cellular level (Patients 1, 2 and 7). One patient (patient 3), showed severely impeded humoral and cellular vaccine responses to the fourth vaccination applied 433 days after administration of the last B-cell targeting treatment (Rituximab).

Conclusions : The most important limitation of this prospective study is its small sample size and the lack of a control group. However, we observed high intra- and interpatient heterogeneity with clear indications of humoral, cellular, or combined response to fourth vaccine in most patients under active treatment. Of note, our observation indicates long-lasting impairment of specific immune responses after a fourth vaccine on both humoral and cellular levels as long as 36 months after last rituximab administration. These findings highlight the need for reliable identification of and development of management strategies for SARS-CoV-2 vaccine non-responders among patients receiving anti-cancer therapies.

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Figure and Table Legend

Figure 1: Cellular and humoral response to fourth SARS-CoV-2 vaccine dose in individual patients including patient characteristics (entity, treatment, time from treatment to vaccination in days). Fold change of specific T-cell proliferation ($CD4^+$, $CD8^+$) after stimulation with spike protein (S) and RBD Hu-1 and total IgG against spike, RBD Hu-1, and RBD Omicron. Fold change >1.1 is considered response to vaccination.

Table 1: Patients‘ characteristics. [1]m = male,[2]COVID-19 vaccines used for homologous or heterologous vaccination regimen: AZD=ChAdOx1, BnT= BNT162b2, Mod= mRNA-1273,[3]Time between third COVID-19 vaccination and blood sampling prior fourth vaccination, [4]Time between fourth COVID-19 vaccination and blood sampling after fourth vaccination,[5]Time between last cancer therapy and fourth COVID-19 vaccination, *FOLFOX = folic acid, 5-fluorouracil plus oxaliplatin,$^+$FERRERI= methotrexate, cytarabine, thiotepa plus rituximab, $^\#$FOLFIRI= folic acid, 5-fluorouracil plus irinotecan

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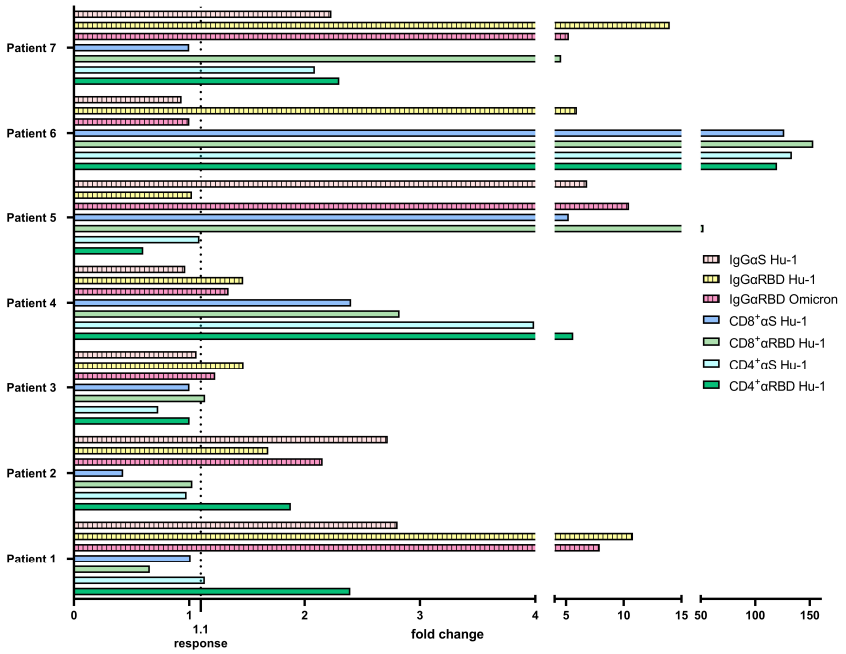
Conflict of Interest: Dr Mair reported receiving nonfinancial support from Pierre Fabre outside the submitted work. Dr Valenta reported receiving personal fees from Viravaxx AG and Worg Pharmaceuticals; receiving grants from HVD Biotech, Viravaxx AG, and Worg Pharmaceuticals outside the submitted work; and holding a patent for Molecular Interaction Assay (pending) and a patent for SARS-CoV-2 vaccine (pending). Dr Preusser reported receiving personal fees from Bayer, Bristol Myers Squibb, Novartis, Gerson Lehrman Group, CMC Contrast, GlaxoSmithKline, Mundipharma, Roche, BMJ Journals, MedMedia, AstraZeneca, AbbVie, Lilly, Medahead, Daiichi Sankyo, Sanofi, Merck Sharp & Dohme, Tocagen, Adastra, and Gan & Lee Pharmaceuticals outside the submitted work. No other disclosures were reported.



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