Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Antibody titres before and after a third dose of the SARS-CoV-2 BNT162b2 vaccine in patients with cancer

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Dear Editor,

Patients with cancer are at increased risk for severe COVID-19 and have reduced humoral immune responses after SARS-CoV-2 infection and dual-dose BNT162b2 vaccination [1,2]. Recently, it was observed that the third dose of BNT162b2 is able to elicit higher SARS-CoV-2 anti-receptor-binding domain (RBD) IgG titres in solid-organ transplant patients and adults aged ≥60 years than two doses [3,4]. Initial reports with limited sample size also indicated that the third BNT162b2 vaccination dose would be beneficial for patients with solid tumour receiving active anti-neoplastic treatment [5–7]. The present study (B-VOICE: EudraCT 2021-000300-38), which is the first large-scale prospective study on humoral responses after a third dose six months post primo vaccination in patients with cancer, confirms that most patients with cancer will elicit a higher humoral response after the third dose of BNT162b2. Quantitative analysis of IgG-antibodies against the SARS-CoV-2 RBD antigen by enzyme-linked immunosorbent assay was performed before the first dose, 28 days and six months after the second dose and 28 days after third BNT162b2 dose in 141 patients with oncohaematological malignacies (Suppl. Table 1). From the 200 initial participants that were included in the B-VOICE study [2], 141 participants were evaluable after the third dose. Drop-out was due to demise (20 participants, 10.0%), postponed vaccination due to illness or disease progression (8 participants, 4.0%), vaccination outside study protocol (5 participants, 2.5%) and consent withdrawal (26 participants, 13.0%).

All subjects were assigned to a cohort based on the treatment type receiving at the time of the third dose administration. Subjects with a solid tumour were divided into four treatment cohorts: chemotherapy, immunotherapy, targeted/hormonal therapy and chemotherapy + immunotherapy. A differentiation for patients with haematological malignancies was made between patients receiving rituximab and patients who have had undergone haematopoietic stem cell transplantation more than one year ago. An additional

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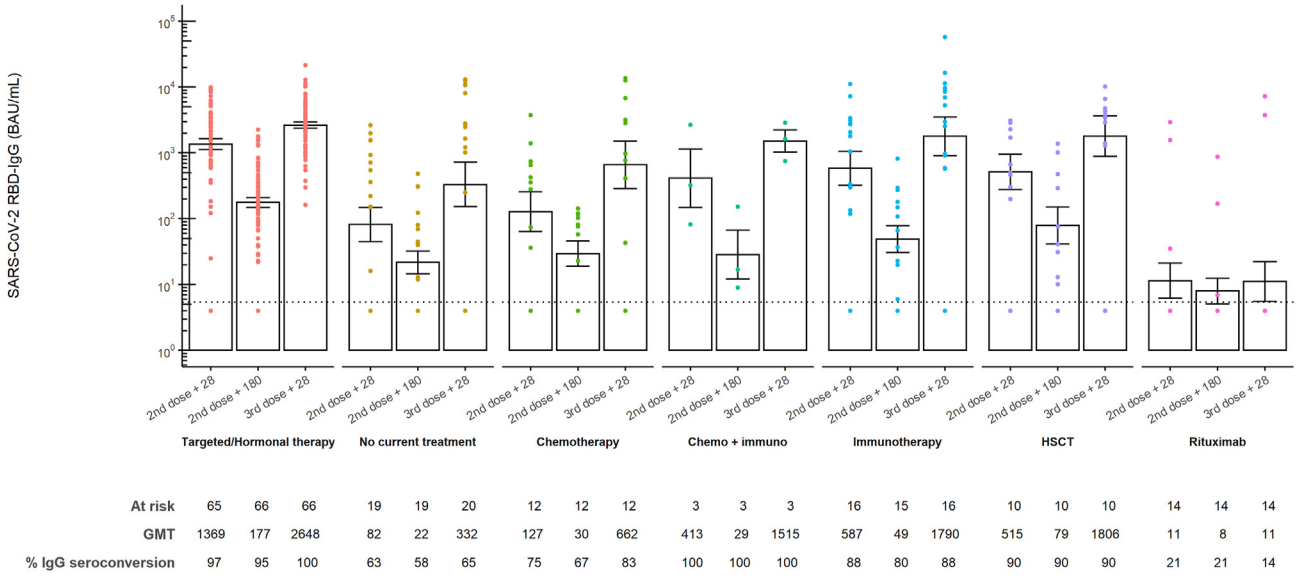

Fig. 1. **SARS-CoV-2 anti-RBD IgG antibody titres before and after a third dose BNT162b2 in patients with cancer.** SARS-CoV-2 anti-receptor-binding domain (RBD) IgG antibody titres 28 days and six months after second BNT162b2 dose and 28 days after third BNT162b2 mRNA COVID-19 vaccine in the different treatment cohorts. Subjects were assigned to treatment cohorts based on the therapy received at the time of the third dose. The height of each bar represents the geometric mean titre (GMT). All samples were analysed using an enzyme-linked immunosorbent assay (ELISA) for the quantitative detection of IgG-class antibodies to RBD (BAU/mL). The dotted line indicates the lower limit of quantification (LLQ) of 5.4 BAU/mL. Values below this detection limit were imputed to half the LLQ. I bars indicate standard errors.

cohort was created for 7 subjects with haematological malignancy and 13 subjects with solid tumours that were no longer receiving active therapy at the time of the third dose. A third BNT162b2 vaccination dose was administered at 183 ± 10 days (6 months) for 97% and 169–200 days for 3% of the subjects, after administration of the second BNT162b2 dose. Log-transformed antibody titres were compared using a random intercept linear mixed model, including time, treatment at the time of sampling and the interaction between time and treatment at the time of sampling.

Anti-RBD IgG titres had waned significantly at six months post-second dose (GMT 65.8BAU/mL [95% CI 48.0–90.2] versus GMT 386.2BAU/mL [95% CI 253.3–588.7], $p < 0.0001$). Administration of a third dose of BNT162b2 induced significantly higher anti-RBD IgG titres 28 days post-third dose than 28 days post-second dose (GMT 936.5BAU/mL [95% CI 600.5–1460.4], versus GMT 386.2BAU/mL [95% CI 253.3–588.7], $p < 0.0001$). In comparison to other treatment cohorts, significantly lower anti-RBD IgG titres 28 days after the second dose and 28 days after the third dose could be observed in the rituximab cohort, with only a few additional seroconverted patients after the third dose (Fig. 1).

A significant decrease in anti-RBD IgG titres at six months post-second BNT162b2 dose was observed in all treatment cohorts. Although waning anti-RBD IgG levels after primo-vaccination are also observed in healthy controls [8], the percentual decrease in anti-RBD IgG titres at six months after primo-vaccination is much lower than the decrease reported in patients with cancer. Considering the investigation that patients with cancer have reduced humoral immune responses after dual-dose BNT162b2 vaccination compared to healthy controls [2], this observation highlights the importance of prioritising the administration of a third vaccination dose in patients with cancer. The significant increase in antibody response upon a third dose is an important observation indicating the successful generation of memory B-cells after primo vaccination [9]. However, in patients receiving rituximab, a third dose hardly induced any humoral immune response as rituximab depletes B-cells [10]. Hence, the role of a third dose remains debatable in this population, although adaptive cellular immunity after vaccination might play a role in protecting these patients against SARS-CoV-2 [10]. In conclusion, most patients after haematopoietic stem cell transplantation or with solid tumours, including those under active anti-cancer treatment, will benefit from the third dose of the BNT16b2 vaccine. However, as a true serological correlate of protection is not yet established, future research on post-vaccine antibody durability should be coupled to the measurement of B-cell and T-cell responses over time.

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Conflict of interest statement

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2021.12.025.

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