In patients with SCLC, a study on prophylactic cranial irradiation with or without hippocampal avoidance has shown that (at least partial) sparing of the uninvolved brain can translate into improved preservation of cognition.[9] The ENCEPHALON trial is investigating the potential cognitive benefit of SRS versus WBRT in patients with SCLC, and is expected to add substantial knowledge in the near future.[10]

In the meantime, the repeated report of equitable overall survival,[7,8] high intracranial control rates, and the convenient possibility of repeated SRS with single or few sessions might be reason enough to offer SRS instead of WBRT to selected patients with limited brain metastases from SCLC.

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Immunogenicity after second and third mRNA-1273 vaccination doses in patients receiving chemotherapy, immunotherapy, or both for solid tumours

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Patients with cancer are at an increased risk of severe COVID-19. Breakthrough infections after two vaccinations do occur and can be lethal.[1–3] Most patients treated for a solid tumour develop an adequate humoral response against SARS-CoV-2 after two vaccinations; however, antibody concentrations tend to be lower when vaccinations are administered during chemotherapy, resulting in a suboptimal response in a small proportion of patients.[4,5] In addition, binding and neutralising antibody concentrations decrease over time, resulting in a further decrease in immunity.[6] This finding prompted many countries to prioritise these patients for a third vaccination. However, little information is available about the immunogenicity of a third vaccination in patients treated for solid tumours, especially against the currently most prevalent variant, omicron (B.1.1.529).[7,8]

In the VOICE trial, we previously reported on safety and humoral and cellular responses 28 days after the second mRNA-1273 (Moderna Biotech, Madrid, Spain) vaccination in patients with solid tumours while receiving immunotherapy (cohort B), chemotherapy (cohort C), or both (cohort D) compared with individuals without cancer (cohort A).[5] Nine (7%) of 131 patients in cohort B, 37 (16%) of 229 patients in cohort C, 16 (11%) of 143 patients in cohort D, and one (<1%) of 240 patients in cohort A, classifying as inadequate responders (previously defined as a binding antibody concentration of ≤300 binding antibody units [BAU]/mL), were eligible to receive a third vaccination after a protocol amendment on Sept 10, 2021 (see appendix pp 4–5 for trial design and study disposition). At the time of the protocol amendment, the benefit of a third vaccination was not yet clear, and it was not

See **Online** for appendix

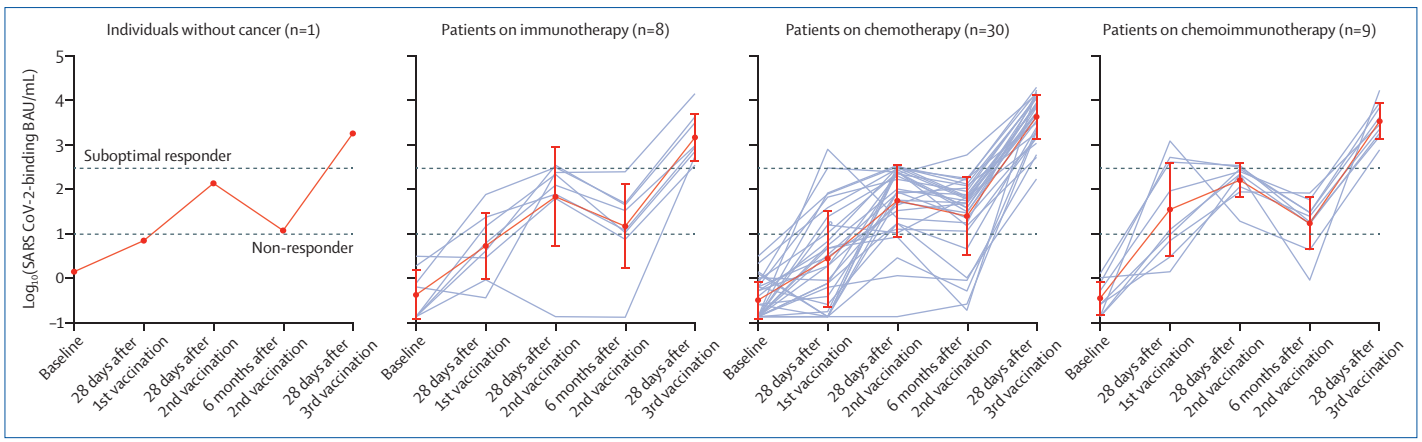

Figure: **SARS-CoV-2-binding antibody response after a third mRNA-1273 COVID-19 vaccination in initially inadequate responders**
The red line connects the geometric means, and the error bars represent geometric SDs. The upper horizontal dashed line indicates 300 BAU/mL threshold for an adequate response, and the lower line indicates the 10 BAU/mL threshold for non-responders. BAU=binding antibody units.

standard policy in the Netherlands, where this study was done.

Here, we report follow-up data—namely, the secondary and exploratory immunogenicity endpoints at 6 months after the second vaccination, including SARS-CoV-2 spike S1-specific serum IgG (hereafter SARS-CoV-2-binding) antibody concentrations in the per-protocol population and, in a subgroup (appendix p 2), spike-specific T cells and virus neutralising antibodies against SARS-CoV-2 D614G (hereafter referred to as wild-type SARS-CoV-2) and against omicron, as previously described.[9] Laboratory assessments, subgroup details, and cancer details can be found in the appendix (pp 2–3). Furthermore, we report breakthrough infections and humoral and cellular responses 28 days after a third mRNA-1273 vaccination in initially inadequate responders and we provide information on safety.

Between 28 days and 6 months after the second vaccination, SARS-CoV-2-binding antibody concentrations and neutralising titres decreased in all cohorts (appendix p 6). At 6 months, the percentage of participants with a binding antibody concentration of more than 300 BAU/mL, previously defined as an adequate response against wild-type SARS-CoV-2 28 days after the second vaccination, was 51% (95% CI 45–58) in cohort A, 32% (24–41) in cohort B, 42% (35–49) in cohort C, and 25% (18–34) in cohort D. At 6 months, a neutralising titre of 40 or more against wild-type SARS-CoV-2 was still detected in most participants (90% [95% CI 70–97] in cohorts A and B, 84% [65–94] in cohort C, and 100% [79–100] in cohort D). The geometric mean titre (GMT) for omicron neutralisation was between 25 times (cohort C) and 77 times (cohort D) lower than for the wild-type variant, with a neutralising titre of 40 or more against omicron in 38% (95% CI 18–65) of participants in cohort A, 67% (35–88) in cohort B, 50% (28–72) in cohort C, and 13% (2–47) in cohorts D (appendix p 6). Spike-specific T cells, measured as spot-forming cells (SFCs) per 10^6 peripheral blood mononuclear cells (PBMCs), decreased by 1·5 times in cohort A, 2·2 times in cohort B, 1·8 times in cohort C, and 3·4 times in cohort D in this period (appendix p 6). At 6 months, 50 or more SFCs per 10^6 PBMCs were found in 75% (95% CI 51–90) of the participants in cohort A, 82% (59–94) in cohort B, 67% (49–81) in cohort C, and 75% (47–91) in cohort D.

In 46 of the 48 evaluable inadequate responders who received the third vaccination, SARS-CoV-2-binding antibody concentrations were higher than 300 BAU/mL after 28 days (figure). Two patients, one in cohort B and one in cohort C, still had a suboptimal response. There were no non-responders (≤10 BAU/mL) after three vaccinations. Although all except one patient in cohort C had a neutralising titre of 40 or more for wild-type SARS-CoV-2, the GMTs for omicron were 22 times lower than for the wild-type variant in cohort B, 27 times lower in cohort C, and 65 times lower in cohort D (appendix p 6). A neutralising titre of 40 or more for omicron was present in 63% (95% CI 31–86) of patients in cohort B, 77% (59–88) in cohort C, and 44% (19–73) in cohort D. After the third vaccination, spike-specific T cells increased by 4·4 times in cohort B, 2·0 times in cohort C,

and 6·0 times in cohort D (appendix p 6), with 50 or more SFCs per 10^6 PBMCs in 71% (95% CI 36–92) of patients in cohort B, 88% (70–96) in cohort C, and 88% (53–98) in cohort D. After the third vaccination, the single individual in cohort A had neutralisation of the wild-type variant, but not omicron, and had 43 SFCs per 10^6 PBMCs.

After the third vaccination, no serious adverse events and no new immune-related adverse events occurred. Local and systemic side-effects were in line with previous vaccinations (appendix p 8). Adverse events of special interest are listed in the appendix (p 9). 14 breakthrough infections, none of which required hospital admission, occurred until the database lock on Dec 28, 2021 (appendix pp 3, 10). These infections coincided with the time that omicron became the dominant variant in the Netherlands. 11 infections occurred in November and December, 2021, and therefore might have been caused by omicron. Our results are in line with those of other studies.[10]

These data show that, after two mRNA-1273 vaccinations, SARS-CoV-2 antibody concentrations and spike-specific T-cell responses decline over time in patients with cancer receiving treatment and in controls. Two vaccinations did not induce neutralising antibodies against omicron in most individuals after 6 months. A third mRNA-1273 vaccination in patients with inadequate antibody response after two vaccinations is safe and effective in increasing immune responses against wild-type SARS-CoV-2, but omicron neutralisation remains poor. Overall, these data show the relevance of a third vaccination for patients being treated for solid cancers.

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