



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.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

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.

SR reports personal fees from AstraZeneca and Accuray, and participation on a Data Safety Monitoring Board or Advisory Board for Accuray.

Stefan Rieken

stefan.rieken@med.uni-goettingen.de

Department of Radiotherapy and Radiation Oncology, University Medical Center Goettingen, 37075 Goettingen, Germany; Comprehensive Cancer Center Lower Saxony, Goettingen, Germany

- 1 Yamamoto M, Serizawa T, Shuto T, et al. Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study. *Lancet Oncol* 2014; **15**: 387–95.
- 2 Chang EL, Wefel JS, Hess KR, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. *Lancet Oncol* 2009; **10**: 1037–44.
- 3 Brown PD, Ballman KV, Cerhan JH, et al. Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCCTG N107C/CEC-3): a multicentre, randomised, controlled, phase 3 trial. *Lancet Oncol* 2017; **18**: 1049–60.
- 4 Soffietti R, Kocher M, Abacioglu UM, et al. A European Organisation for Research and Treatment of Cancer phase III trial of adjuvant whole-brain radiotherapy versus observation in patients with one to three brain metastases from solid tumors after surgical resection or radiosurgery: quality-of-life results. *J Clin Oncol* 2013; **31**: 65–72.
- 5 Baumert BG, Rutten I, Dehing-Oberije C, et al. A pathology-based substrate for target definition in radiosurgery of brain metastases. *Int J Radiat Oncol Biol Phys* 2006; **66**: 187–94.
- 6 Paz-Ares L, Dvorkin M, Chen Y, et al. Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. *Lancet* 2019; **394**: 1929–39.
- 7 Gaebe K, Li Y, Park A, et al. Stereotactic radiosurgery versus whole brain radiation therapy in patients with intracranial metastatic disease and small cell lung cancer: a systematic review and meta-analysis. *Lancet Oncol* 2022; May 26. [https://doi.org/10.1016/S1470-2045\(22\)00271-6](https://doi.org/10.1016/S1470-2045(22)00271-6).
- 8 Rusthoven CG, Yamamoto M, Bernhardt D, et al. Evaluation of first-line radiosurgery vs whole-brain radiotherapy for small cell lung cancer brain metastases: the FIRE-SCLC cohort study. *JAMA Oncol* 2020; **6**: 1028–37.
- 9 Rodríguez de Dios N, Couñago F, Murcia-Mejía M, et al. Randomized phase III trial of prophylactic cranial irradiation with or without hippocampal avoidance for small-cell lung cancer (PREMER): a GICOR-GOECF-SEOR Study. *J Clin Oncol* 2021; **39**: 3118–27.
- 10 Bernhardt D, Hommertgen A, Schmitt D, et al. Whole brain radiation therapy alone versus radiosurgery for patients with 1–10 brain metastases from small cell lung cancer (ENCEPHALON trial): study protocol for a randomized controlled trial. *Trials* 2018; **19**: 388.

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



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

Published Online
April 25, 2022
[https://doi.org/10.1016/S1470-2045\(22\)00203-0](https://doi.org/10.1016/S1470-2045(22)00203-0)

See Online for appendix

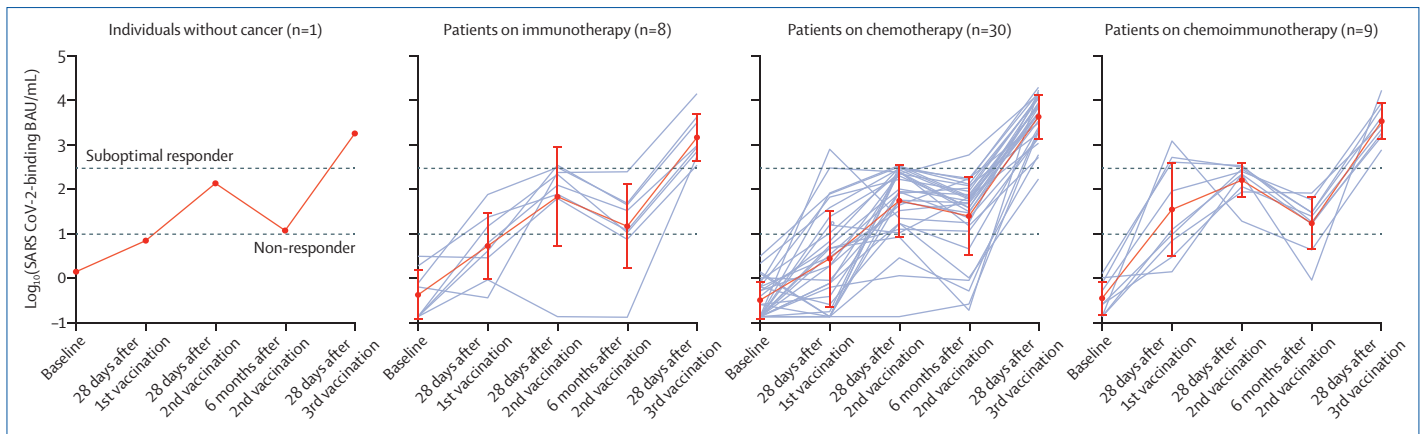


Figure: SARS-CoV-2-binding antibody response after a third mRNA-1273 COVID-19 vaccination in initially inadequate responders. The red line connects the geometric means, and the error bars represent geometric SDs. The upper horizontal dashed line indicates 300 BAU/mL threshold for an adequate response, 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 cohort D (appendix p 6). Spike-specific T cells, measured as spot-forming cells (SFCs) per 10⁶ 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 10⁶ 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 10⁶ 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 10⁶ 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.

SFO reports research grants from Novartis and Celldex Therapeutics, and consultancy fees from Bristol Myers Squibb (BMS; all paid to the institution). AAMvdV reports consultancy fees from BMS, Merck Sharp & Dohme (MSD), Merck, Sanofi, Eisai, Pfizer, Ipsen, Roche, Pierre Fabre, and Novartis, and travel support from Bayer, Roche, Novartis, and Pfizer (all paid to the institution). A-MCD reports consultancy fees from Roche, Boehringer Ingelheim, Amgen, Bayer, Pharmamar, and Sanofi (all paid to the institution); speaker fees from Eli Lilly, AstraZeneca, Jansen, Chiesi, and Takeda (all paid to the institution); and research support from BMS, AbbVie, and Amgen (all paid to the institution). EFS reports consultancy fees from Eli Lilly (all paid to the institution); speaker fees from AstraZeneca, Boehringer Ingelheim, and Daiichi Sankyo (all paid to the institution); and advisory board fees from AstraZeneca, Bayer, BMS, MSD, Merck, Novartis, Pfizer, Roche Genentech, Roche Diagnostics, and Takeda (all paid to the institution). TJNH reports advisory board fees from BMS, AstraZeneca, Merck, Pfizer, Roche, and MSD (all paid to the institution). MJ reports consultancy fees from AstraZeneca and Pierre Fabre (all paid to the institution). GFR reports funding from the Alexander von Humboldt Foundation (paid to the institution). JBAGH reports consultancy fees from Achilles Therapeutics, BioNTech, BMS, Immunocore, Instil Bio, Molecular Partners, MSD, Gadeta, Merck Serono, Neogene Therapeutics, Novartis, Pfizer, PokeAcel, Roche/Genentech, Sanofi, and T-Knife (paid to the institution); consultancy fees from Neogene Tx; speaker fees from Ipsen, Eisai, and Novartis

(paid to the institution); research grants from Asher-Bio, BMS, BioNTech, MSD, and Novartis (paid to the institution); and stock in Neogene Tx. EGEdV reports an advisory role at Daiichi Sankyo, NSABP, and Sanofi, and research funding from Amgen, AstraZeneca, Bayer, Chugai Pharma, Crescendo, CytomX Therapeutics, G1 Therapeutics, Genentech, Nordic Nanovector, Radius Health, Regeneron, Roche, Servier, and Synthron (all paid to the institution). All other authors declare no competing interests. The study is funded by ZonMw, the Netherlands Organisation for Health Research and Development. SFO and AAMvdV contributed equally.

*Sjoukje F Oosting, *Astrid A M van der Veldt, Rudolf S N Fehrmann, Corine H GeurtsvanKessel, Rob S van Binnendijk, Anne-Marie C Dingemans, Egbert F Smit, T Jeroen N Hiltermann, Gerco den Hartog, Mathilda Jalving, Tatjana T Westphal, Arkajyoti Bhattacharya, Faye de Wilt, Annemarie Boerma, Lisanne van Zijl, Guus F Rimmelzwaan, Pia Kvistborg, Cecile A C M van Els, Nynke Y Rots, Debbie van Baarle, John B A G Haanen, Elisabeth G E de Vries*

a.vanderveldt@erasmusmc.nl

Department of Medical Oncology (SFO, RSNF, MJ, ABh, EGEdV), Department of Pulmonary Diseases (TJNH), and Department of Medical Microbiology and Infection Prevention (ABo, DvB), University Medical Centre Groningen, University of Groningen, Groningen, Netherlands; Department of Medical Oncology (AAMvdV), Department of Radiology and Nuclear Medicine (AAMvdV), Department of Viroscience (CHG, FdW), and Department of Respiratory Medicine (A-MCD), Erasmus Medical Centre, 3015 GD Rotterdam, Netherlands; Centre for Infectious Disease Control, National Institute for Public Health and the Environment, Bilthoven, Netherlands (RSvB, GDH, CACMvE, NYR); Department of Thoracic Oncology (EFS), Department of Medical Oncology (LvZ, JBAGH), and Department of Molecular Oncology and Immunology (PK), Netherlands Cancer Institute, Amsterdam, Netherlands; Netherlands Comprehensive Cancer Organization, Utrecht, Netherlands (TTW); Research Centre for Emerging Infections and Zoonoses, University of Veterinary Medicine Hannover, Hannover, Germany (GFR); Department of Biomolecular Health Sciences, Faculty of Veterinary Medicine, Utrecht University, Utrecht, Netherlands (CACMvE)

- Schmidt AL, Labaki C, Hsu C-Y, et al. COVID-19 vaccination and breakthrough infections in patients with cancer. *Ann Oncol* 2021; **33**: 340–46.
- Fendler A, Shepherd STC, Au L, et al. Immune responses following third COVID-19 vaccination are reduced in patients with hematologic malignancies compared to patients with solid cancer. *Cancer Cell* 2022; **40**: 114–16.
- Hippisley-Cox J, Coupland CAC, Mehta N, et al. Risk prediction of covid-19 related death and hospital admission in adults after covid-19 vaccination: national prospective cohort study. *BMJ* 2021; **374**: n2244.
- Peeters M, Verbruggen L, Teuwen L, et al. Reduced humoral immune response after BNT162b2 coronavirus disease 2019 messenger RNA vaccination in cancer patients under antineoplastic treatment. *ESMO Open* 2021; **6**: 100274.
- Oosting SF, van der Veldt AAM, GeurtsvanKessel CH, et al. mRNA-1273 COVID-19 vaccination in patients receiving chemotherapy, immunotherapy, or chemoimmunotherapy for solid tumours: a prospective, multicentre, non-inferiority trial. *Lancet Oncol* 2021; **22**: 1681–91.
- Levin EG, Lustig Y, Cohen C, et al. Waning immune humoral response to BNT162b2 Covid-19 vaccine over 6 months. *N Engl J Med* 2021; **385**: e84.
- Ligumsky H, Dor H, Etan T, et al. Immunogenicity and safety of BNT162b2 mRNA vaccine booster in actively treated patients with cancer. *Lancet Oncol* 2022; **23**: 193–95.
- Fendler A, Shepherd STC, Au L, et al. Omicron neutralising antibodies after third COVID-19 vaccine dose in patients with cancer. *Lancet* 2022; **399**: 905–07.
- GeurtsvanKessel CH, Geers D, Schmitz KS, et al. Divergent SARS CoV-2 Omicron-reactive T and B cell responses in COVID-19 vaccine recipients. *Sci Immunol* 2022; **7**: eabo2202.
- Fendler A, de Vries EGE, GeurtsvanKessel CH, et al. COVID-19 vaccines in patients with cancer: immunogenicity, efficacy and safety. *Nat Rev Clin Oncol* 2022; published online March 11. <https://doi.org/10.1038/S41571-022-00610-8>.