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.

Omicron neutralising antibodies after third COVID-19 vaccine dose in patients with cancer

Patients with cancer are at greater risk of severe COVID-19 and have been prioritised for COVID-19 vaccination globally. We previously showed that following two doses of COVID-19 vaccines, neutralising antibody (nAb) responses against the B.1.1.7 (alpha), B.1.351 (beta), and B.1.617.2 (delta) variants of concern (VOCs) are decreased compared to the wild type (WT) SARS-CoV-2, particularly in patients with blood cancer.[1] More recently, we reported that following a third vaccine dose, nAb responses to these VOCs increase in most patients with cancer, including those with no or waning response following two vaccine doses.[2] Since November, 2021, the B.1.1.529 (omicron) VOC has rapidly become the dominant SARS-CoV-2 VOC globally. Omicron partially evades vaccine-induced immunity,[3] but a third vaccine dose increases omicron nAb responses in the general population.[4–6] Comparable data in patients with cancer are lacking, leaving patients and cancer physicians without the means to calibrate infection risk[7] while maintaining necessary cancer treatments. We used live-virus micro-neutralisation assays to evaluate response to omicron following three doses of COVID-19 vaccine in participants of the CAPTURE study (NCT03226886), a prospective, longitudinal cohort of patients with cancer.

We evaluated 199 patients with cancer, 115 (58%) of whom had solid cancer and 84 (42%) blood cancer, all of whom received a third dose of BNT162b2 (appendix p 1) after two doses of either BNT162b2 (33%) or ChAdOx1 (67%). A matched sample obtained before the third dose was also evaluated in 179 of 199 patients (100 of 115 patients with solid cancer; 79 of 84 with blood cancer). The median time between the second and third doses was 176 days (IQR 166–188). 23 of 199 patients had a history of SARS-CoV-2 infection, all before the second vaccine dose, and none with omicron. nAb titres (nAbT) against delta and omicron were measured at a median of 11 days (IQR 0–78) before and 23 days (19–29) after the third vaccine dose. As described previously for this assay, nAbT was categorised as undetectable (<40, the lower limit of detection) or detectable (>40).[1,8,9]

Among the 100 patients with solid cancer, after two vaccine doses, nAbT against omicron was detectable in 37 (37%) patients (appendix p 4), whereas nAbT against delta was detectable in 56 (56%) patients (McNemar test, p=0·0002) and nAbT against WT SARS-CoV-2 was detectable in 97 (97%) patients (p<0·0001).[2] Among the 115 patients with solid cancer who had a third vaccine dose, nAbT against omicron was detectable in 104 (90%) patients, whereas nAbT against delta was detectable in 112 (97%) patients (p=0·013), and nAbT against WT SARS-CoV-2 was detectable in 114 (99%) patients (p=0·0044).[2]

Among 79 patients with blood cancer, after two vaccine doses, nAbT against omicron was detectable in 15 (19%) patients (appendix p 4), whereas nAbT against delta was detetable in 31 (39%) patients (McNemar test, p=0·0002) and nAbs against WT SARS-CoV-2 was detectable in 31 (89%) patients (p<0.0001).[2] Among the 84 patients who received a third vaccine dose, nAbs against omicron was detectable in 47 (56%) patients, whereas nAbT against delta was detectable in 60 (71%) patients (p=0.0009), and nAbT against WT SARS-CoV-2 was detectable in 72 (86%) patients (p<0·0001).[2] Considering the 64 of 79 patients with blood cancer who had undetectable nAbT against omicron after two vaccine doses, 29 (45%) developed nAbs against omicron after the third dose, indicating effective boosting in many patients. The nAbT against omicron correlated with nAbT against WT SARS-CoV-2 and delta, respectively (appendix p 4) but were consistently lower.

Overall, our data from patients with cancer highlight the higher immune evasive capacity of omicron than delta, which is consistent with the observations in the general population. We found that a third vaccine dose boosted the neutralising response against omicron in patients with cancer, but the effect was blunted in patients with blood cancer compared to those with solid cancer.

Multivariable logistic regression analysis (appendix p 3) confirmed that after three doses, detectable nAbT against omicron was significantly associated with cancer type (solid *vs* blood cancer odds ratio [OR] 7·51 [95% CI 4·05–14·63], p<0·001) but not age, sex, or the vaccine type administered as first and second dose (BNT162b2 *vs* ChAdOx1).

In a separate multivariable logistic regression analysis, we considered only patients with blood cancer. Treatment with anti-CD20 monoclonal antibodies within 12 months, and Bruton's tyrosine kinase inhibitors (BTKi) within 28 days of the third vaccine dose was significantly associated with undetectable nAbT against omicron (OR 0·04 [95% CI 0·003–0·21], p=0·0074. None of ten patients who received anti-CD20 and one of five patients who received BTKi had detectable nAbT against omicron following three vaccine doses. The presence of progressive disease versus complete response following the most recent anticancer treatment was also significantly associated with undetectable NAbT against omicron (OR 0·08 [95% CI 0·01–0·46], p=0·027). Blood cancer subtype, vaccine type administered as first and second dose, and age were not significantly associated with detectable NAbT against omicron.

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See Online for appendix

Finally, we evaluated omicron nAbT in four patients with a history of breakthrough delta infection after two vaccine doses. The time from the second vaccine dose to infection ranged from 112 to 176 days. COVID-19 symptoms were mild (n=3 patients, WHO COVID-19 severity index 2–3, including fever [n=2], coryza [n=2], cough [n=2]), and one patient was asymptomatic. None of the patients had detectable nAbT against omicron or delta[2]) before infection. Following infection, all patients developed detectable nAbT against omicron (as well as delta[2]; appendix p 5), suggesting that two vaccine doses and a third antigenic challenge via delta infection can lead to a functional immune response against omicron.[6]

There are limitations to our study. Additional subgroup analyses were limited by the heterogeneity and size of the blood cancer cohort and will require more patients. The exact correlates of immune protection against VOC remain undefined; however, multiple studies have shown that higher nAbT correlate with reduced risk of symptomatic infection.[10,11] Finally, we did not evaluate vaccine-induced cellular responses to omicron as we had for other VOCs.[2] We note that emerging reports suggest T-cell responses against omicron remain comparable to ancestral variants in the general population without cancer.[12,13]

In conclusion, we show that most of the patients with cancer in the CAPTURE cohort lacked detectable nAbT against omicron following two vaccine doses, independent of the vaccine type. A third dose of BNT162b2 resulted in a significant increase in patients with nAbT against omicron. Whereas only a few patients with solid cancer lacked nAbT against omicron after three vaccine doses, a substantial proportion of patients with blood cancer, especially those on B-cell-depleting therapies or with progressive cancer, did not mount a detectable response. We previously showed that T-cell responses against delta are detected in patients with cancer even in the absence of humoral response.[1] T cells probably continue to offer a degree of protection against severe COVID-19, and we note that ancestral SARS-CoV-2-specific T cells cross-recognise omicron.[12] Given the high transmissibility and current prevalence of omicron, continued mask-wearing, physical distancing, and vaccination of close contacts will be crucial to protecting patients with blood cancer. Further, early treatment with neutralising monoclonal antibodies[6] or antivirals might be beneficial and are being deployed to vulnerable patient groups in the UK.[14] The incremental benefit of a third vaccine dose in boosting nAb responses in patients with blood cancer lends support for a fourth dose in this population, as per UK guidance at the time of writing.

For **UK guidance on booster vaccine** see https://www.nhs.uk/conditions/coronavirus-covid-19/coronavirus-vaccination/coronavirus-booster-vaccine/

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*Annika Fendler, Scott T C Shepherd, Lewis Au, Mary Wu, Ruth Harvey, Andreas M Schmitt, Zayd Tippu, Benjamin Shum, Sheima Farag, Aljosja Rogiers, Eleanor Carlyle, Kim Edmonds, Lyra Del Rosario, Karla Lingard, Mary Mangwende, Lucy Holt, Hamid Ahmod, Justine Korteweg, Tara Foley, Taja Barber, Andrea Emslie-Henry, Niamh Caulfield-Lynch, Fiona Byrne, Daqi Deng, Svend Kjaer, Ok-Ryul Song, Christophe Queval, Caitlin Kavanagh, Emma C Wall, Edward J Carr, Simon Caidan, Mike Gavrielides, James I MacRae, Gavin Kelly, Kema Peat, Denise Kelly, Aida Murra, Kayleigh Kelly, Molly O'Flaherty, Robyn L Shea, Gail Gardner, Darren Murray, Nadia Yousaf, Shaman Jhanji, Kate Tatham, David Cunningham, Nicholas Van As, Kate Young, Andrew J S Furness, Lisa Pickering, Rupert Beale, Charles Swanton, Sonia Gandhi, Steve Gamblin, David L V Bauer, George Kassiotis, Michael Howell, Emma Nicholson, Susanna Walker, James Larkin, *Samra Turajlic, on behalf of the CAPTURE consortium*
samra.turajlic@crick.ac.uk

Cancer Dynamics Laboratory (AF, STCS, LA, ZT, BS, TB, AE-H, NC-L, FB, DD, ST), High Throughput Screening Laboratory (MW, O-RS, CQ, CK, ECW, MH), Worldwide Influenza Centre (RH), Structural Biology Scientific Technology Platform (SK), Cell Biology of Infection Laboratory (EJC, RB), Safety, Health & Sustainability (SC), Scientific Computing Scientific Technology Platform (MG), Metabolomics Scientific Technology Platform (JIM), Department of Bioinformatics and Biostatistics (GKe), Cancer Evolution and Genome Instability Laboratory (CS), Neurodegeneration Biology Laboratory (SGan), Structural Biology of Disease Processes Laboratory (SGam), RNA Virus Replication Laboratory (DLVB), Retroviral Immunology Laboratory (GKa), The Francis Crick Institute,

London NW1 1AT, UK; Skin and Renal Units (STCS, LA, AMS, ZT, BS, SF, AR, EC, KE, LDR, KL, MM, LH, HA, JK, TF, KP, DK, AM, KK, MO'F, KY, AJSF, LP, JL, ST); Department of Pathology (RLS, GG, DM), Lung Unit (NY), Acute Oncology Service (NY), Anaesthetics, Perioperative Medicine and Pain Department (SJ, KT, SW), Gastrointestinal Unit (DC), Clincal Oncology Unit (NVA), Haemato-oncology Unit (EN), The Royal Marsden NHS Foundation Trust, London, UK; University College London Hospitals NHS Foundation Trust Biomedical Research Centre, London, UK (ECW); Translational Cancer Biochemistry Laboratory (RLS) and Melanoma and Kidney Cancer Team (ST), Institute of Cancer Research, London, UK; Division of Medicine, University College London, London, UK (RB); University College London Cancer Institute, London, UK (CS); UCL Queen Square Institute of Neurology, London, UK (SGan)

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