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.
Most patients with blood cancer have reduced humoral and cellular immunity against SARS-CoV-2 variants following COVID-19 vaccination, so they are at increased risk of severe outcomes from COVID-19 infection and contribute disproportionately to ongoing COVID-19-related mortality. As most restrictions to curb the spread of COVID-19 have lifted, this vulnerable patient group relies on existing COVID-19 therapeutics, including monoclonal antibodies (mAb) and antivirals, in both pre- and post-exposure contexts. However, ongoing evolution of Spike in Omicron subvariants has reduced neutralizing capacity of mAb therapies in laboratory assays, leading the World Health Organization (WHO) and the US Food and Drug Administration (FDA) to recommend against the use of some of these agents. Antiviral therapies such as nirmatrelvir and ritonavir (Paxlovid) are likely to retain activity against current Omicron subvariants, but they are
contraindicated in patients receiving cytochrome P450 (CYP) 3A4 or P-glycoprotein-interacting therapies thus limiting their use in those receiving corticosteroids, antifungals, and many systemic anticancer therapies. Taken together, vulnerable patient groups are left with few therapeutic options, and this highlights a requisite for continual surveillance and re-assessment of available products in a rapidly evolving SARS-CoV-2 variant landscape.

We report follow-up findings from CAPTURE (NCT03226886)—a prospective longitudinal cohort study assessing functional immune responses following infection and vaccination in patients with cancer. We previously reported that a proportion of patients with blood cancer do not have detectable neutralizing antibody titers (NAbTs) against Omicron variants even after four vaccine doses. Here, we developed an in vitro assay utilizing acoustic liquid dispensing technology to accurately transfer nanoliter concentrations of concentrated mAbs at clinically relevant concentrations into the sera of 79 patients with blood cancer (Table S1) vaccinated with three and/or fourth vaccine doses (BNT162b2), then measured the resulting NAbTs against Omicron variants in our good clinical practice (GCP)-compliant high-throughput live-virus microneutralization assay. Sera of 116 patients with solid cancer after three vaccine doses (BNT162b2) were used as controls (Table S1).

To establish the neutralizing activity of the licensed mAb therapies, we generated extensive dose-response curves using over 300 data points per mAb and determined EC90 values with tight 95% confidence intervals (CI) against Omicron BA.1, BA.5, BQ.1.1, XBB, and more recently XBB.1.5. We tested the following mAbs and their licensed combinations: Sotrovimab; Casirivimab, Imdevimab, together as Ronapreve; and Gilagivimab, Tixagevimab, together as Evusheld. Sotrovimab is the only product that retains neutralizing capacity against all tested Omicron variants (Figure S1A) with EC90s that are below or within the range of serum pharmacokinetic (PK) concentrations as measured in early phase clinical studies (Figure S1B).8

Based on the results above and our previous report that patients with blood cancer had suboptimal NAbTs against Omicron variants after three or four vaccine doses, we chose to spike Sotrovimab, Gilagivimab, and Tixagevimab into the sera of patients with blood cancer at their reported PK maximum concentration (Cmax) and concentration at 28 days (C28d) (Figure S1C). A small proportion of patients (11% [9/79]) had undetectable binding antibodies to ancestral SARS-CoV-2 S1 following four vaccine doses. However, in patient sera spiked with phosphate buffered saline (PBS), a larger proportion of patients had undetectable or weak (<40) NAbTs after three (BA.1: 34% [26/77], BA.5: 31% [24/77], BQ.1.1: 34% [26/77], and XBB: 10% [8/77]) or four (BA.1: 22% [17/79], BA.5: 24% [19/79], BQ.1.1: 32% [25/79], and XBB: 6% [5/79]) vaccine doses against a majority of variants tested. As NAbTs are predictive of protection against a variant, an increase by an mAb would be beneficial to these patients, with bigger fold changes (FCs) in NAbTs providing better protection. Sotrovimab robustly increased NAbTs against BA.1 (median FC[IQR]: 3.34[1.89–6.05]) and XBB (median FC[IQR]: 5.94[3.67–14.43]) at Cmax with expected lower increases at C28d (BA.1 median FC[IQR]: 1.45[1.16–2.30] and XBB median FC[IQR]: 1.84[1.16–3.40]). In contrast, we observed a moderate increase against BA.5 (Cmax median FC[IQR]: 2.25[1.29–3.28]) and only a small increase against BQ.1.1 (Cmax median FC[IQR]: 1.75[1.10–2.32]). Gilagivimab increased NAbTs against BA.5 (Cmax median FC[IQR]: 2.09[1.28–3.78]) but only increased NAbTs against BA.1 in patients that had no detectable NAbTs prior to spike-in. Tixagevimab did not increase NAbTs against any variants despite displaying neutralizing activity against BA.1 (Figure S1A), which is consistent with our calculated EC90 and corresponding 95% CI that extends well above the reported Cmax range (Figure S1B). Overall, the spike-in data reflect our EC90 estimations as well as when the mAbs are run independently by being spiked into non-neutralizing fetal bovine serum (FBS) (black bars in Figure S1C), suggesting that either EC90s with tight 95% CIs or mAbs run independently at Cmax concentration on an inhibitory dilution scale can be used to infer activity in sera. Importantly, spike-in led to a consistent increase in NAbTs, especially in patients with low or undetectable NAbTs after three or four vaccine doses, and these titers are better or comparable to NAbTs detected in patients with solid cancer after three vaccine doses without spike-in (gray-dashed line and shading in Figure S1C). The contribution of the mAb to the overall NABT is difficult to assess, but in these data, an mAb only increased NAbTs if the serum spiked with PBS has an NABT below that of the mAb alone spiked into FBS.

When we completed the above experiments, the WHO designated XBB.1.5 as a variant of interest (VOI) based on rising cases across the globe and reports of increased transmissibility. In response to this, we acquired XBB.1.5 and tested the panel of mAbs. In our results, Sotrovimab has a slightly better EC50 against XBB.1.5 than XBB (Figure S1A and Table S1B) and an EC90 between that of XBB and BA.5 (Figure S1B and Table S1B). As already shown above, the spike-in data directly reflect our EC90 estimations; therefore, we can conservatively infer that spiking in Sotrovimab at Cmax would boost the NABTs of patients with blood cancer to levels between what we see for BA.5 and XBB (median NABT between ~200 and 1000, Figure S1C). When we ran the spike-in experiment, this was indeed the expected boost against XBB.1.5 despite lower starting serum NABTs in these patients (PBS spike-in), leading to a much higher FC when Sotrovimab is spiked in (Sotrovimab at Cmax median FC[IQR]: 5.48[3.04–10.95], Figure S1C).

Since the lifting of restrictions, multiple Omicron subvariants now co-circulate through populations, making it more difficult to acquire data at pace and assess which treatments remain effective for vulnerable patients. While only a handful of patients in this study had undetectable anti-S binding Ab (accessible routinely in clinical practice), the proportion with undetectable NABTs to Omicron subvariants was higher, so identifying patients with suboptimal responses in the clinic remains a challenge. Our in vitro data demonstrate that Sotrovimab retains neutralizing activity against representative circulating Omicron variants at clinically relevant concentrations in patients with blood cancer with suboptimal vaccine response. Furthermore, our data support the recent National Institute for Clinical Excellence (NICE) recommendation for use of Sotrovimab in...
patients with early COVID-19 where there is a contraindication to nirmatrelvir and ritonavir. Ongoing clinical research is required to establish protective efficacy of NAbT in vivo, but given the pace of Omicron subvariant emergence, high-quality in vitro data enable the rapid evaluation of these vital therapeutics against emerging SARS-CoV-2 variants and provide informative data for the assessment of their use.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.ccell.2023.04.005.

ACKNOWLEDGMENTS

This research was funded in part by the National Institute for Health Research (NIHR) Biomedical Research Centre at the Royal Marsden NHS Foundation Trust (RMCC32) and Cancer Research UK (CRUK) (grant reference number C50947/A18178). This work was supported by the Francis Crick Institute, which receives its core funding from CRUK (FC001988, FC001218, FC001099, FC001002, FC001078, FC001169, FC001030, FC011104, and CC2230), the UK Medical Research Council (FC001988, FC001218, FC001099, FC001002, FC001078, FC001169, FC001030, FC011104, and CC2230), the Wellcome Trust (FC001988, FC001218, FC001099, FC001002, FC001078, FC001169, FC001030, FC011104, and CC2230), the UK Research and Innovation, and the UK Medical Research Council (MR/W005611/1). TRACERx Renal is partly funded by the NIHR Biomedical Research Centre at University College London Hospitals, the CRUK University College London Centre, the Experimental Cancer Medicine Centre, and the Breast Cancer Research Foundation (BCRF 20-157). This work was supported by a Stand Up To Cancer (SU2C)-LUNGevity-American Lung Association Lung Cancer Intervention Dream Team Translational research grant (grant number SU2C-AACR-DT23-17 to S.M. Dubinett and A.E. Spirito). SU2C is a division of the Entertainment Industry Foundation. Research grants are administered by the American Association for Cancer Research for Cancer Research, the scientific partner of SU2C. C. Swanton received an ERC Advanced Grant (PROTEUS) from the European Research Council under the European Union’s Horizon 2020 research and innovation program (grant agreement number 835297). C. Swanton is a Royal Society Napier Research Professor (RP150154). For the purpose of Open Access, the author has applied a CC BY public copyright licence to any Author Accepted Manuscript version arising from this submission.

DECLARATION OF INTERESTS

The authors declare no competing interests.

REFERENCES