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Letter

Sotrovimab restores neutralization against current Omicron subvariants in patients with blood cancer

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Most patients with blood cancer have reduced humoral and cellular immunity against SARS-CoV-2 variants following COVID-19 vaccination,[1,2] so they are at increased risk of severe outcomes from COVID-19 infection and contribute disproportionately to ongoing COVID-19-related mortality.[3] 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.[4] 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.[5] Here, we developed an *in vitro* assay utilizing acoustic liquid dispensing technology to accurately transfer nanoliters of concentrated mAbs at clinically relevant concentrations into the sera of 79 patients with blood cancer (Table S1) vaccinated with a third and/or fourth vaccine dose (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 Cilgavimab, 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).[6]

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, Cilgavimab, and Tixagevimab into the sera of patients with blood cancer at their reported PK maximum concentration (C_{max}) and concentration at 28 days (C_{28d}) (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 C_{max}, with expected lower increases at C_{28d} (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 (C_{max} median FC [IQR]: 2.25[1.29–3.28]) and only a small increase against BQ.1.1 (C_{max} median FC[IQR]: 1.75[1.10–2.32]). Cilgavimab increased NAbTs against BA.5 (C_{max} 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 C_{max} 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 concentrations 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.[7] 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 C_{max} 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 C_{max} 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-S1 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.[8] Ongoing clinical research is required to establish protective efficacy of NAbT *in vivo*[9,10], 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.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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