



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.

Letter

Activity of AZD7442 (tixagevimab-cilgavimab) against Omicron SARS-CoV-2 in patients with hematologic malignancies

Robert Stuver,¹ Gunjan L. Shah,² Neha S. Korde,³ Lindsey E. Roeker,⁴ Anthony R. Mato,⁴ Connie L. Batlevi,¹ David J. Chung,² Sital Doddi,⁵ Lorenzo Falchi,¹ Boglarka Gyurkocza,² Audrey Hamilton,¹ Ya-Hui Lin,⁵ Ann A. Jakubowski,² Erel Joffe,¹ Heather L. Landau,² Richard J. Lin,² Sham Mailankody,³ M. Lia Palomba,¹ Jae H. Park,⁴ Miguel-Angel Perales,² Doris M. Ponce,² Lakshmi V. Ramanathan,⁵ Gilles A. Salles,¹ Michael Scordo,² Susan K. Seo,⁶ Urvi A. Shah,³ Eytan M. Stein,⁴ David Straus,¹ Saad Z. Usmani,³ James W. Young,² Andrew D. Zelenetz,¹ Ariela Noy,^{1,8,*} and Santosha A. Vardhana^{1,7,8,*}

¹Lymphoma Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA

²Adult Bone Marrow Transplant Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA

³Myeloma Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA

⁴Leukemia Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA

⁵Department of Laboratory Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA

⁶Infectious Disease Service, Division of Subspecialty Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA

⁷Human Oncology and Pathogenesis Program, Memorial Sloan Kettering Cancer Center, New York, NY, USA

⁸These authors contributed equally

*Correspondence: noya@mskcc.org (A.N.), vardhans@mskcc.org (S.A.V.)

<https://doi.org/10.1016/j.ccell.2022.05.007>

Despite therapeutic advances against SARS-CoV-2, including multiple vaccines, oral antiviral therapies, and monoclonal antibodies, patients with hematologic malignancies remain at increased risk for complications secondary to SARS-CoV-2 (Vijenthira et al., 2020). Before vaccines for SARS-CoV-2 were available, a meta-analysis of over 3,300 patients with hematologic malignancies and COVID-19 showed a 34% risk of death (Vijenthira et al., 2020). Even with vaccination, mortality is over 10%, and recent reports have demonstrated increased risk of SARS-CoV-2 infection, hospitalization, and death secondary to COVID-19 in vaccinated patients with hematologic malignancies, especially in those receiving B cell depleting therapy (Pagano et al., 2022).

Accordingly, pre-exposure prophylaxis is a critical component in the care of patients with hematologic malignancies. In the United States, the combined monoclonal product AZD7442/Evusheld (tixagevimab-cilgavimab) has been granted emergency use authorization (EUA) in individuals 12 years and older who have a moderate to severe immunocompromising condition and may not mount an adequate vaccination response (<https://www.fda.gov/media/154701/download>). Authorization stems from a recently published randomized, placebo-controlled trial (PROVENT, NCT04625725) of over 5,000 adults who had not received

SARS-CoV-2 vaccination at the time of AZD7442 administration (Levin et al., 2022). Patients randomized to the treatment arm received a single dose (150 mg of tixagevimab and 150 mg of cilgavimab). With a median follow-up at 83 days, receipt of AZD7442 resulted in a 77% reduction in symptomatic COVID-19 ($p < 0.001$, 95% confidence interval [CI] 46–90) and a 69% reduction in symptomatic COVID-19 or death from any cause ($p = 0.002$, 95% CI 36–85).

Notably, this trial was conducted before the emergence of the Omicron variant (B.1.1.529 lineage) of SARS-CoV-2 in late 2021. In addition, although PROVENT included patients who were at risk for inadequate vaccine response, only 7% of participants had cancer or a history of cancer. We therefore evaluated the efficacy of AZD7442 in patients who had hematologic malignancies and who had been treated at Memorial Sloan Kettering Cancer Center (MSKCC), and our evaluation included measurement of anti-SARS-CoV-2 spike protein antibody titers and plasma neutralizing activity against the Omicron variant after AZD7442 administration.

Adult patients at MSKCC who had hematologic malignancies participated in this prospective observational study. AZD7442 was administered according to the EUA Fact Sheet, initially with a single 150 mg dose. In the midst of the study,

the FDA authorized revision to dosing given concerns of reduced activity against certain Omicron subvariants. Patients subsequently received either a second 150 mg dose in the setting of a prior dose or 300 mg in those without prior treatment.

Anti-SARS-CoV-2 spike protein (S) IgG antibody levels were measured before and roughly one month after administration of AZD7442 (median: 33 days). Measurement of anti-S IgG antibodies was performed using the AdviseDx SARS-CoV-2 IgG II assay (Abbott). Virus neutralization was measured using the SARS-CoV-2 surrogate virus neutralization test kit (Genscript), and percent inhibition was calculated per manufacturer's instructions with a positive cutoff value of 30%. Full methods are described in the [Supplemental Methods](#).

The study was conducted in accordance with the Declaration of Helsinki guidelines and approved by the Institutional Review and Privacy Board of Memorial Hospital/MKSCC. Patients provided consent for research specimens.

Clinical characteristics are described in [Table S1](#). We evaluated 52 patients with hematologic malignancies. The most common diagnosis was non-Hodgkin lymphoma (38.5%). Nearly one-half (46.2%) had received prior stem cell transplant or chimeric antigen receptor T cell therapy. 47 (90.4%) received a



single 150 mg dose of AZD7442; 17 of those received an additional 150 mg dose. Five (9.6%) received a single 300 mg dose.

Samples were collected at a median of 33 days after administration of a single 150 mg dose (Figure S1A). All patients achieved uniformly high anti-S IgG titers (median 16,099.3 AU/mL) after administration of a single 150 mg dose (Figure S1B). Plasma from all patients treated with a single 150 mg dose achieved uniform and complete neutralization of wild-type (WT) receptor-binding domain (RBD); however, the median neutralizing activity against Omicron-RBD failed to reach the positive cutoff value of 30% (Figure S1C, in 30/47 patients). Five patients treated with a second 150 mg dose and five patients treated with a single 300 mg dose were also studied (Figure S1D). Plasma from these patients achieved significantly higher neutralization of Omicron-RBD ($p = 0.003$) compared with a single 150 mg dose, and nine of 10 patients achieved neutralizing capacity above the positive cutoff value (Figure S1E).

With a median follow-up time of 79 days after first administration, two patients (3.8%) had documented SARS-CoV-2 infection; both had received a single 150 mg dose. One patient tested positive 8 days after AZD7442 administration, and the other tested positive 30 days after administration. Both were symptomatic, received sotrovimab, and recovered without hospitalization or death (Table S1).

These results are a dedicated evaluation of AZD7442 in patients with hematologic malignancies. Results show that AZD7442 failed to achieve meaningful neutralization of Omicron-RBD in patients with hematologic malignancies who were treated with a single 150 mg dose. Neutralization significantly increased above the positive cutoff after a single 300 mg dose, but it remained heterogeneous. Anti-S IgG titers after a single dose of AZD7442 were consistent with activity against WT SARS-CoV-2, but notably did not correlate with neutralizing capacity against Omicron.

These results confirm preliminary reports that suggested differential neutralizing capacity of therapeutic antibodies against various Omicron sublineages (Bruel et al., 2022; Takashita et al., 2022;

VanBlargan et al., 2022). Compared with early SARS-CoV-2 strains, the Omicron variant has at least 33 mutations in its spike protein, including 15 in the RBD—the primary target for monoclonal therapies (Qin et al., 2021). These mutations allow for antibody evasion that can hinder the efficacy of currently available monoclonal therapies (Iketani et al., 2022). Accordingly, AZD7442, which was developed and studied before emergence of the Omicron variant, has reduced activity against the current dominant strain. These results nevertheless support the revised 300 mg dose of AZD7442 pre-exposure prophylaxis.

Despite its dampened activity against the Omicron variant, AZD7442 remains the only available pre-exposure prophylaxis agent. Vigilant behavior and vaccination when physiologically appropriate therefore remain the backbone of protection against SARS-CoV-2 in patients with hematologic malignancies (Chung et al., 2021; Tamari et al., 2021). Identification and development of broadly neutralizing antibody therapies that target highly conserved regions of the SARS-CoV-2 spike protein are needed in the face of a readily mutable pathogen.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at <https://doi.org/10.1016/j.ccell.2022.05.007>.

ACKNOWLEDGMENTS

We thank Mr. and Mrs. Richard Worden for their generous contribution to this study.

AUTHOR CONTRIBUTIONS

R.S., A.N., and S.A.V. designed the research and wrote the manuscript. S.D., Y.L., L.V.R., and S.A.V. performed the experiments and analysis. R.S., G.L.S., N.S.K., A.R.M., L.E.R., C.L.B., D.J.C., L.F., B.G., A.H., A.A.J., E.J., H.L.L., R.J.L., S.M., M.L.P., J.H.P., M.A.P., D.M.P., G.A.S., M.S., U.A.S., S.K.S., E.M.S., D.S., S.Z.U., J.W.Y., A.D.Z., and A.N. cared for the patients. All authors provided critical feedback and reviewed the final manuscript.

DECLARATION OF INTERESTS

The authors report no competing interests related to the research. S.A.V. is an advisor for Immunai and previously consulted for ADC Therapeutics and Koch Disruptive Technologies. A.N. is an advisor for Janssen, Morphosys, and Epizyme, has consulted for Physician Education Resource, has received honoraria from Medscape and Pharmacyclics, and has received research funding from Pharmacyclics and Rafael Pharmaceuticals.

REFERENCES

- Bruel, T., Hadjadj, J., Maes, P., Planas, D., Seve, A., Staropoli, I., Guivel-Benhassine, F., Porrot, F., Bolland, W.H., Nguyen, Y., et al. (2022). Serum neutralization of SARS-CoV-2 Omicron sublineages BA.1 and BA.2 in patients receiving monoclonal antibodies. *Nat. Med.* <https://doi.org/10.1038/s41591-022-01792-5>.
- Chung, D.J., Shah, G.L., Devlin, S.M., Ramanathan, L.V., Doddi, S., Pessin, M.S., Hoover, E., Marcello, L.T., Young, J.C., Boutemine, S.R., et al. (2021). Disease- and therapy-specific impact on humoral immune responses to COVID-19 vaccination in hematologic malignancies. *Blood Cancer Discov.* 2, 568–576.
- Iketani, S., Liu, L., Guo, Y., Liu, L., Chan, J.F., Huang, Y., Wang, M., Luo, Y., Yu, J., Chu, H., et al. (2022). Antibody evasion properties of SARS-CoV-2 Omicron sublineages. *Nature* 604, 553–556.
- Levin, M.J., Ustianowski, A., De Wit, S., Launay, O., Avila, M., Templeton, A., Yuan, Y., Seegobin, S., Ellery, A., Levinson, D.J., et al. (2022). Intramuscular AZD7442 (Tixagevimab-Cilgavimab) for Prevention of Covid-19. *N. Engl. J. Med.* Online Ahead of Print. <https://doi.org/10.1056/NEJMoa2116620>.
- Pagano, L., Salmanton-Garcia, J., Marchesi, F., Lopez-Garcia, A., Lamure, S., Itri, F., Gomes-Silva, M., Dragonetti, G., Falces-Romero, I., van Doesum, J., et al. (2022). COVID-19 in vaccinated adult patients with hematological malignancies: preliminary results from EPICOVIDEHA. *Blood* 139, 1588–1592.
- Qin, S., Cui, M., Sun, S., Zhou, J., Du, Z., Cui, Y., Fan, H., et al. (2021). Genome Characterization and Potential risk Assessment of the Novel SARS-CoV-2 variant Omicron (B.1.1.529). *Zoonoses* 1, 1–5. <https://doi.org/10.15212/ZOONOSES-2021-0024>.
- Takashita, E., Kinoshita, N., Yamayoshi, S., Sakai-Tagawa, Y., Fujisaki, S., Ito, M., Iwatsuki-Horimoto, K., Halfmann, P., Watanabe, S., Maeda, K., et al. (2022). Efficacy of antiviral Agents against the SARS-CoV-2 Omicron Subvariant BA.2. *N. Engl. J. Med.* 386, 1475–1477.
- Tamari, R., Politikos, I., Knorr, D.A., Vardhana, S.A., Young, J.C., Marcello, L.T., Doddi, S., Devlin, S.M., Ramanathan, L.V., Pessin, M.S., et al. (2021). Predictors of Humoral response to SARS-CoV-2 vaccination after Hematopoietic cell Transplantation and CAR T-cell therapy. *Blood Cancer Discov.* 2, 577–585.
- VanBlargan, L.A., Errico, J.M., Halfmann, P.J., Zost, S.J., Crowe, J.E., Jr., Purcell, L.A., Kawaoka, Y., Corti, D., Fremont, D.H., Diamond, M.S., et al. (2022). An infectious SARS-CoV-2 B.1.1.529 Omicron virus escapes neutralization by therapeutic monoclonal antibodies. *Nat. Med.* 28, 490–495.
- Vijenthira, A., Gong, I.Y., Fox, T.A., Booth, S., Cook, G., Fattizzo, B., Martin-Moro, F., Razanamahery, J., Riches, J.C., Zwicker, J., et al. (2020). Outcomes of patients with hematologic malignancies and COVID-19: a systematic review and meta-analysis of 3377 patients. *Blood* 136, 2881–2892.