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Letter

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

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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.

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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.

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Supplemental information

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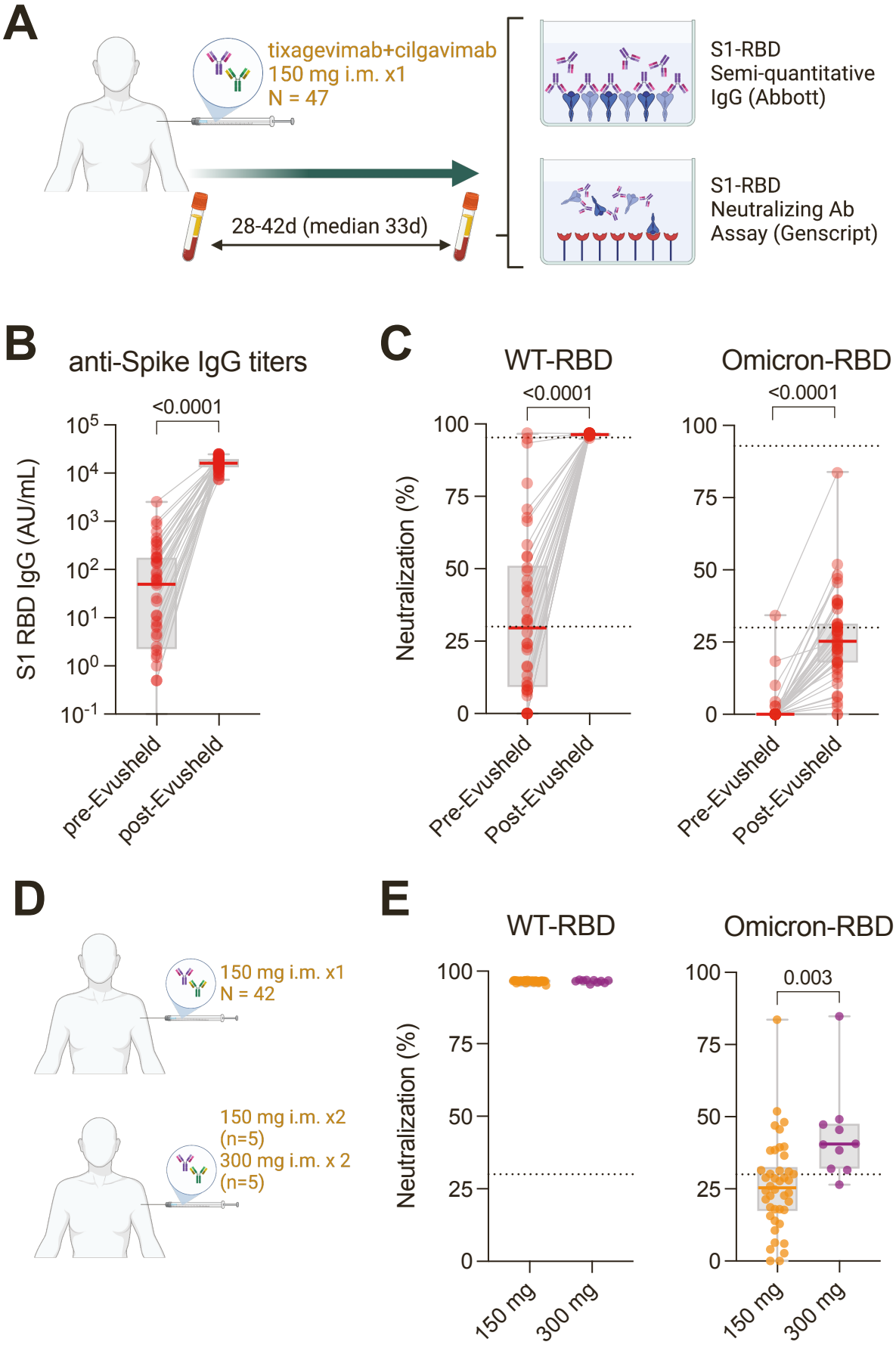
A
tixagevimab+cilgavimab
150 mg i.m. x1
N = 47
28-42d (median 33d)
S1-RBD
Semi-quantitative
IgG (Abbott)
S1-RBD
Neutralizing Ab
Assay (Genscript)
B
anti-Spike IgG titers
<0.0001
S1 RBD IgG (AU/mL)
pre-Evusheld
post-Evusheld
C
WT-RBD
Omicron-RBD
<0.0001
<0.0001
Neutralization (%)
Pre-Evusheld
Post-Evusheld
Pre-Evusheld
Post-Evusheld
D
150 mg i.m. x1
N = 42
150 mg i.m. x2
(n=5)
300 mg i.m. x 2
(n=5)
E
WT-RBD
Omicron-RBD
0.003
Neutralization (%)
150 mg
300 mg
150 mg
300 mg

Figure S1. AZD7442/Evusheld (Tixagevimab + Cilgavimab) administration results in heterogeneous protection against the SARS-CoV-2 Omicron variant.

A. Treatment, sample collection schedule, and correlative assay schema for 47 patients with hematologic malignancies who received tixagevimab + cilgavimab at the 150 mg dose. B. Patients retained uniformly high anti-Spike IgG titers 1 month after receipt of Tixagevimab + Cilgavimab. C. Uniform and complete neutralization of wildtype (WT) receptor-binding domain (RBD), but not Omicron variant RBD, by plasma collected from Tixagevimab + Cilgavimab treated patients. D. Treatment schema for patients receiving 300 mg of Tixagevimab + Cilgavimab. 5 of the 47 patients monitored as in A. received a second dose of 150 mg, while an additional 5 patients received a single dose of 300 mg. E. Significantly higher but still heterogeneous neutralization of Omicron-RBD by a 300 mg dose of Tixagevimab + Cilgavimab. For box-and-whisker plots, box hinges are at 25^{th} and 75^{th} percentile of distribution, midline is at median value, and whiskers mark minimum and maximum values.

Table S1. Clinical Characteristics and Outcomes.

Characteristic	Cohort (n = 52)
Median age (range) – years	62 (35–89)
Disease – no. (%)*	
AML	6 (11.5)
ALL	2 (3.8)
CLL	15 (28.8)
MM	8 (15.4)
NHL	20 (38.5)
Other†	3 (5.8)
Prior cellular therapy – no. (%)	
any	24 (46.2)
autologous transplant	11 (21.2)
allogeneic transplant	10 (19.2)
CAR T-cell therapy	13 (25.0)
Prior SARS-CoV-2 infection – no. (%)	5 (9.6)
Prior SARS-CoV-2 vaccination doses – no. (%)	
any (≥ 1)	48 (92.3)
two	42 (80.8)

three	32 (61.5)
four	3 (5.8)
Dose of AZD7442 received – no. (%)	
150 mg once	30 (57.7%)
150 mg twice	17 (32.7%)
300 mg once	5 (9.6%)
Post-dose outcomes – no. (%)	
SARS-CoV-2 infection	2 (3.8)
COVID-19 treatment	2 (3.8)
COVID-19 hospitalization	0 (0.0)
COVID-19 death	0 (0.0)

*1 patient with AML and MM.
†Other includes 1 patient with essential thrombocythemia, 1 patient with myelodysplastic syndrome, and 1 patient with Waldenstrom macroglobulinemia.
ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; CAR, chimeric antigen receptor; CLL, chronic lymphocytic leukemia; COVID-19, coronavirus disease 2019; mg, milligram; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; no., number; SARS-CoV-2, severe acute respiratory distress syndrome coronavirus 2.

Supplemental Methods

Patient selection

Based on initial limited availability of AZD7442, patients eligible for therapy included those who had received treatment for a hematologic malignancy (including CAR T cell therapy and/or hematopoietic stem cell transplant) within the previous six months, had moderate or severe primary immunodeficiency, or who were unable to receive COVID-19 vaccination for medical reasons. In addition, patients must have had an anti-S IgG less than 1000 AU/mL measured ≥ two weeks after last administered COVID-19 vaccination. All patients had received at least one vaccination. All requests for AZD7442 were reviewed expeditiously by designated faculty. Patients included in the presented study included those who had received AZD7442 and had a scheduled blood draw for medical reasons roughly one month after administration. The first 52 patients meeting this criterion were assayed. The research was conducted through the Division of Hematologic Malignancies at MSKCC under IRB protocol 20-390 (COVID-19 infection and Cancer) in accordance with the Declaration of Helsinki guidelines.

Anti–SARS-CoV-2 Spike IgG Assay

A chemiluminescent microparticle immunoassay (AdviseDx SARS-CoV-2 IgG II assay; Abbott) detected anti–SARS-CoV-2 spike IgG antibody titers. Briefly, serum samples were combined with paramagnetic particles coated with recombinant SARS-CoV-2 protein specific for the RBD of the S1 protein, followed by incubation, washing, and addition of a conjugate and chemiluminescent substrate. The resulting chemiluminescent reaction was measured as a relative light unit (RLU), with a direct relationship between the amount of IgG antibodies to SARS-CoV-2 in the sample and the RLU detected by the system optics (Architect i2000 analyzer).

Surrogate Virus Neutralization Assay

The SARS-CoV-2 surrogate virus neutralization test kit (Genescript) measured circulating neutralizing antibodies against SARS-CoV-2 that block the interaction between the RBD of the viral spike glycoprotein with the ACE2 cell-surface receptor. Briefly, serum samples were preincubated with the horseradish peroxidase (HRP)–conjugated recombinant SARS-CoV-2 RBD fragment (either WT-RBD, wild-type variant, or Omicron-RBD, Omicron variant) to allow binding of circulating RBD-specific neutralization antibodies, then added to a capture plate precoated with the human ACE2 receptor (hACE2) protein, followed by additional incubation and washing steps before addition of a stop solution for endpoint reaction reading on a microplate reader at 450 nm. The absorbance of the sample is inversely dependent on the titer of the anti–SARS-CoV-2 neutralizing antibodies. Percentage inhibition was calculated per manufacturer's instructions with a positive cutoff value of 30% and validated with a panel of confirmed COVID-19 patient and healthy control sera. This value was determined from a comparator plaque-reduction neutralization test (PRNT) assay performed per World Health Organization guidelines, showing 100% agreement with $PRNT_{50}$ and $PRNT_{90}$ levels.

Statistical analysis

The effect of AZD7442 on anti-Spike IgG titers, neutralization of SARS-CoV-2 WT-RBD, and SARS-CoV-2 Omicron-RBD was assessed using a paired t-test. Neutralization of Omicron-RBD by AZD7442 in patients receiving 150 mg vs 300 mg was assessed using an unpaired t-test.