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Supplemental information

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

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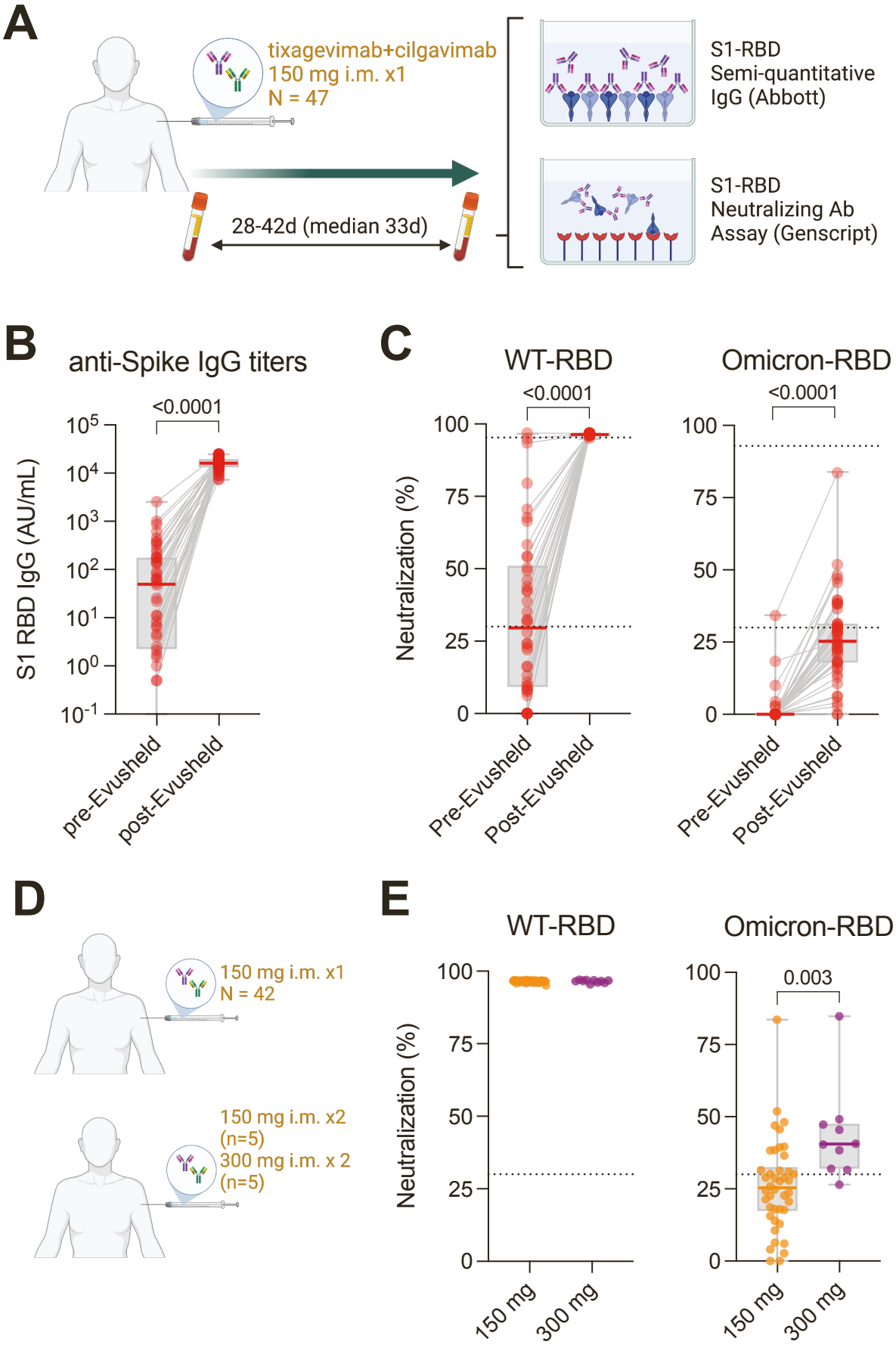
A
tixagevimab+cilgavimab
150 mg i.m. x1
N = 47
28-42d (median 33d)
S1-RBD
Semi-quantitative
IgG (Abbott)
S1-RBD
Neutralizing Ab
Assay (Genscript)
B
anti-Spike IgG titers
<0.0001
S1 RBD IgG (AU/mL)
pre-Evusheld
post-Evusheld
C
WT-RBD
Omicron-RBD
<0.0001
<0.0001
Neutralization (%)
Pre-Evusheld
Post-Evusheld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