Predictors of SARS-CoV-2 Omicron breakthrough infection after receipt of AZD7442 (tixagevimab-cilgavimab) for pre-exposure prophylaxis among hematologic malignancy patients

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Abstract

AZD7442 (tixagevimab-cilgavimab) is a combination of two human monoclonal antibodies for pre-exposure prophylaxis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection among high-risk patients who do not mount a reliable vaccine response. Foremost among these are hematologic malignancy patients with limited clinical trial or real-world experience to assess the effectiveness of this combination treatment since the emergence of Omicron and its subvariants. We performed a retrospective study of 892 high-risk hematologic malignancy patients who received AZD7442 at Memorial Sloan Kettering Cancer Center in New York City from January 1, 2022 to July 31, 2022. We evaluated demographic, clinical, and laboratory characteristics and performed regression analyses to evaluate risk factors for breakthrough infection. We also evaluated the impact of updated AZD7442 dosing regimens on the risk of breakthrough infection. Among 892 patients, 98 (10.9%) had a breakthrough infection during the study period. A majority received early outpatient treatment (82%) and eventually eight (8.2%) required hospitalization for management of Coronavirus Disease 2019 (COVID-19), with a single instance of severe COVID-19 and death. Patients who received a repeat dose or a higher first-time dose of AZD7442 had a lower incidence of breakthrough infection. Univariate analyses did not reveal any significant predictors of breakthrough infection. While AZD7442 is effective at reducing SARS-CoV-2 breakthrough infection in patients with hematologic malignancies, no risk factors reliably predicted risk of infection. Patients who received updated dosing regimens as per Food and Drug Administration guidelines had better protection against breakthrough infection.

Introduction

While vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has helped to reduce Coronavirus Disease 2019 (COVID-19)-related morbidity and mortality, individuals with underlying immune dysfunction remain at high risk for not achieving target immunological and clinical outcomes. For example, serological assessments after two or three primary mRNA vaccine doses demonstrated an abrogated seroconversion rate among cancer patients or early waning of immunity, especially among patients with hematologic malignancies.[1-3]

Subsequent studies found that vaccinated immunocompromised patients have higher odds of breakthrough infection and increased risk of severe disease leading to hospitalization and death compared to non-immunosuppressed patients.[3,4] Furthermore, although data on variant-specific breakthrough among cancer patients are sparse, neutralizing activity of serum from vaccinated individuals is diminished against the Omicron subvariants.[6-9]

In December 2021, during the peak of the Omicron surge, the US Food and Drug Administration (FDA) granted emergency use authorization (EUA) to AZD7442, a combination of two human monoclonal antibodies for pre-exposure prophylaxis against COVID-19 in high-risk patients.[10] The use of AZD7442 to prevent SARS-CoV-2 infection was the standard of care throughout 2022 for high-risk patients when regional variants retained susceptibility to this agent. AZD7442 was one of just a few medical innovations to be included in Times Magazine's "The Best Inventions of 2022".[11] However, a vital gap in the trials leading to AZD7442's EUA was the minimal representation of high-risk cancer patients.[12] Shortly after its initial authorization, neutralization assays revealed decreased activity of AZD7442 against emerging Omicron subvariants.[13,14] Subsequently, the FDA authorized revisions to the AZD7442 dosing regimen given concerns of reduced potency to certain Omicron subvariants. However, the EUA was rescinded on January 26, 2023, when the prevalence of susceptible variants in the US was less than 10%.[15]

The present study describes the incidence, predictors, and clinical outcomes among AZD7442-treated hematologic malignancy patients for the first 8 months after this drug received EUA for primary prevention of SARS-CoV-2 infection in high-risk patients.

Methods

Study population

From January 1, 2022, to July 31, 2022, all consecutive patients at Memorial Sloan Kettering Cancer Center (MSKCC) >=12 years of age who received AZD7442 were included in the study. A retrospective analysis of 892 AZD7442 recipients was conducted. Identification of case patients and their medical background and clinical course from COVID-19 were extracted from the electronic medical record. The MSKCC Institutional Review Board granted a Health Insurance Portability and Accountability Act waiver of authorization to conduct this study.

Laboratory methods

SARS-CoV-2 RNA test

Viral RNA was detected using nasopharyngeal swabs or saliva samples as previously described.[16] Briefly, SARS-CoV-2 RNA was tested for by real-time reverse transcription-polymerase chain reaction (RT-PCR) using several commercial assays. These included the Cobas® SARS-CoV-2 test (Roche Molecular Diagnostics, Indianapolis, Indiana USA), the TaqPath™ COVID-19 Combo Kit (Thermo Fisher Scientific, Waltham, MA), the ePlex Respiratory Panel 2 (GenMark/Roche Molecular Diagnostics, Indianapolis, IN), and the BioFire Respiratory Panel 2.1 (BioMerieux, Salt Lake City, UT). Anti-SARS-CoV-2 spike IgG antibody assay was performed as previously described.[17]

SARS-CoV-2 whole genome sequencing

Whole genome sequencing (WGS) was performed on samples with a cycle threshold (Ct) value <30 to increase the likelihood of successful sequencing. Samples from platforms that do not provide a Ct value (i.e., BioFire RP 2.1 and ePlex 2) underwent WGS without knowledge of Ct value. WGS was performed as previously described using the ARTIC protocol with version 4.1 primers (Integrated DNA Technologies [IDT (Integrated DNA Technologies)], Coralville, Iowa USA).[18] Pangolin software (https://github.com/cov-lineages/pangolin) was used to assign lineages for each consensus sequence using the Pango nomenclature.

Statistical analysis

Baseline demographic and clinical characteristics for all study patients were reported as absolute frequency and percentage or median with interquartile range (IQR). Due to revised guidance from the FDA on AZD7442 dosing, study patients received varied dosing during the evaluation period. Therefore, we classified our study patients into four groups based on the dosage of AZD7442 they received: group 1 received one dose 150-150 mg, group 2 received two doses of 150-150 mg, group 3 received one dose of 150-150 mg and one dose 300-300 mg, and group 4 received one dose of 300-300 mg. Crude estimates of treatment effect were stratified by dose groups. The number of breakthrough infections, total number of person-days, and incidence rate per 1,000 person-days for each stratum were calculated. Follow-up person-days began from the initial date of AZD7442 administration until the SARS-CoV-2 breakthrough date, death, or the end of the study period. Incidence rate ratios (95% confidence interval [CI]) were calculated to assess the association between breakthrough infection by dose group.

In order to examine the relationship between breakthrough infection and AZD7442 dosage, we performed extended Cox regression analyses using a counting process data structure to account for the varying dosages administered at different time periods. For each dose group, univariable Cox regression analyses were performed to evaluate potential risk factors for breakthrough infection. Variables that were significant at $P<0.05$ in the univariable analysis were considered for the multivariable cox regression model.

Results

Baseline characteristics of AZD7442 recipients (study cohort)

During the study period, 892 high-risk hematologic malignancy patients received AZD7442. The median age was 68 years (IQR, 59-75), 410 (46.0%) were female, and the underlying cancers were lymphoma (57.2%), leukemia/myelodysplastic syndrome (MDS) (28.8%), myeloma/amyloidosis (13.5%), and others (0.1%). One hundred ninety-six patients (21.9%) had received hematopoietic stem cell transplantation (HSCT) or chimeric antigen receptor (CAR) T-cell therapy within 1 year (Table 1). Almost 40% of patients had received anti-CD20 therapy within the previous 12 months. Dose groups 1, 2, 3, and 4 were comprised of 149 (16.7%), 292 (32.7%), 75 (8.4%), and 376 (42.2%) patients, respectively. Four hundred eighty-three (54.1%) patients were vaccinated. Patients were considered fully vaccinated ≥2 weeks

Table 1. Demographics and baseline characteristics of study patients.

Characteristic	Total [a, b] N=892
Age in years, median (IQR)	68 (59-75)
Female sex, N (%)	410 (46.0)
Laboratory values, N (%)	
Creatinine ≥1.1 mg/dL[c]	238 (26.9)
Creatinine <1.1 mg/dL[c]	648 (73.1)
Lymphocyte ≥500 cell/mcL[d]	794 (89.3)
Lymphocyte <500 cell/mcL[d]	95 (10.7)
$CD3^+CD4^+$ (T4 helper) cells, blood ≥200 cell/mcL[e]	182 (61.3)
$CD3^+CD4^+$ (T4 helper) cells, blood <200 cell/mcL[e]	115 (38.7)
CD19 ≥50 cell/mcL[e]	61 (20.9)
CD19 <50 cell/mcL	231 (79.1)
Neutrophils ≥0.5 k/mcL[f]	763 (98.5)
Neutrophils <0.5 k/mcL[f]	12 (1.5)
Total IgG ≥500 mg/dL	44 (53.1)
Total IgG <500 mg/dL	39 (47.0)
Anti-Spike SARS CoV-2 antibody levels (Abbot), N (%)	
Spike Ab ≥1,000 AU/mL[g]	81 (10.0)
Spike Ab <1,000 AU/mL[g]	731 (90.0)
COVID-19 vaccination status, N (%)	
≥3 vaccine doses (Yes)[h]	483 (54.1)
<3 vaccine doses (No)[h]	409 (45.9)
Comorbidities,[i] N (%)	
At least one co-morbidity	503 (56.3)
No co-morbidity	389 (43.6)
Atrial fibrillation (Yes)	107 (12.0)
Atrial fibrillation (No)	785 (88.0)
Chronic lung disease (Yes)	47 (5.2)
Chronic lung disease (No)	845 (94.7)
Heart failure (Yes)	42 (4.7)
Heart failure (No)	850 (95.3)
HIV (positive)	8 (0.9)
HIV (negative)	884 (99.1)
Hypertension (Yes)	378 (42.4)
Hypertension (No)	514 (57.6)
Diabetes (Yes)	91 (10.2)
Diabetes (No)	801 (89.8)
Renal failure (Yes)	167 (18.7)
Renal failure (No)	725 (81.3)
Systemic steroids (Yes),[j] N (%)	199 (22.3)
Systemic steroids (No),[j] N (%)	693 (77.7)
Anti-CD20 therapy (Yes),[k] N (%)	349 (39.1)
Anti CD20 therapy (No),[k] N (%)	543 (60.9)

Characteristic	Total [a, b] N=892
Cancer types, N (%)	
Leukemia/myelodysplastic syndrome	257 (28.8)
Myeloma/amyloidosis	120 (13.5)
Other	1 (0.1)
Lymphoma	510 (57.2)
Chemotherapy (Yes),[l] N (%)	549 (61.6)
Chemotherapy (No),[l] N (%)	343 (38.5)
Relapse/refractory disease (Yes), N (%)	179 (20.1)
Relapse/refractory disease (No), N (%)	713 (79.9)
BMT CAR T (Yes),[m] N (%)	196 (22.0)
BMT CAR T (No),[m] N (%)	696 (78.0)
Body mass index,[n] N (%)	
Underweight (< 18.5)	22 (2.5)
Healthy weight (18.5-24.9)	318 (35.7)
Overweight (25.0-29.9)	347 (39.0)
Obese (≥30.0)	204 (22.9)

Ab: antibody; BMT: bone marrow transplant; CAR T: chimeric antigen receptor T-cell therapy; IgG: immunoglobulin G; HIV: human immunodeficiency virus; IQR: interquartile range. [a]Clinical classifications were based on available data. [b]Odds ratios and *P* values were calculated from logistic regression applying Firth's correction, where appropriate. [c]Creatinine, IgG: most recent values before first AZD7442 start date within the last 6 months. [d]Lymphocytes: most recent 3 laboratory values within 12 months prior to first AZD7442 start date. All 3 counts must be <500 per microliter to be in the '<500' category. At least 1 count of value ≥500 per microliter is considered in the "≥500" category. One patient did not have 3 laboratory values prior to COVID-19 diagnosis. [e]CD4, CD19: most recent values before first AZD7442 start date within the last year. [f]Neutrophils: most recent values before first AZD7442 start date within 1 month. [g]Spike antibody: most recent test value before first AZD7442 start date within 1 year. [h]Vaccination history (N): charts were manually reviewed for patients with no vaccine history. [i]Chronic conditions (atrial fibrillation, chronic lung disease [chronic obstructive pulmonary disease, bronchiectasis, asthma], heart failure, hypertension, human immunodeficiency virus (HIV), diabetes, renal failure) were based on ICD10 diagnosis codes within 12 months of the study period. [j]Systemic steroids (dexamethasone, methylprednisolone, hydrocortisone, prednisone): given within 30 days prior to first AZD7442 start date. [k]Anti-CD-20 therapy (rituximab, obinutuzumab, tafasitamab, hyaluroinidase-rituximab, ofatumumab): given within previous 12 months of AZD7442. [l]Chemotherapy during study period. [m]BMT and CAR T-cell therapies combined with service dates within 1 year of the study period. [n]BMI: most recent value during past 12 months.

after the final dose of a primary vaccination series.[19] Five hundred and three (56.3%) patients had at least one additional comorbidity as outlined in Table 1.

Incidence and clinical outcomes of breakthrough infection in AZD7442 recipients

Ninety-eight (10.9%) unique patients had breakthrough infection from SARS-CoV-2 during the study period. Among these patients with breakthrough infection, the median age was 65 years (IQR, 53-74) and 37 (37.7%) were female. The underlying cancers included hematologic malignancy patients only: lymphoma (57.1%), leukemia/MDS (35.7%), and myeloma/amyloidosis (7.1%). Twenty-seven breakthrough patients had received HSCT or CAR T-cell therapy. The median time from the first AZD7442 administration to laboratory diagnosis of COVID-19 was 104 days (range, 4-198; IQR, 67-140). Fifty-five (56.1%) patients were vaccinated, and 52 (53.0%) patients had at least one additional medical comorbidity. Dose groups 1 and 2 were each comprised of 35 (35.7%) patients while dose group 4 was comprised of 26 (26.5%) patients. Only 2 (2.0%) patients were in dose group 3.

The incidence of breakthrough infection was highest in dose group 1 at 1.60 per 1,000 person days compared to 0.70, 0.15, 0.86 per 1,000 person days in dose groups 2, 3 and 4, respectively. Compared to dose group 1, the incidence rate ratio (IRR) was 0.43 (95% CI: 0.26-0.72), 0.09 (95% CI: 0.01-0.36), and 0.54 (95% CI: 0.32-0.92) for dose groups 2, 3, and 4, respectively (Table 2).

Univariate analyses for patients in three of the four dosing groups did not show significant predictors for breakthrough infection. In particular, anti-CD20 therapy within the previous 12 months, a known risk factor for suboptimal binding and neutralizing antibody response, was not an independent predictor of infection in any dose group.[20,21] Although neutrophil count was significant for patients in dose group 4, the low number of cases with absolute neutrophil count (ANC) <500/mcL and the small hazard ratio precluded meaningful statistical comparison (Table 3). Due to the limited number of significant predictors, multivariable analyses were not performed. Notable risk factors that did not predict breakthrough infection across all four dose groups included age, medical comorbidities, vaccination status, underlying cancer type, and prior HSCT or CAR T-cell therapy.

Clinical outcomes of breakthrough infection and time to breakthrough infection by Omicron subvariants

The clinical presentation and outcome of the 98 patients with breakthrough infection from SARS-CoV-2 are summarized in Table 4. Most received standard-of-care therapy with authorized monoclonal antibody therapy (n=47, 47.9%) or antivirals, most commonly nirmatrelvir-ritonavir (n=31, 31.6%). Eight patients (8.2%) were hospitalized for the management of COVID-19, of which two were hospitalized elsewhere without available records. The illness severity was mild to moderate for five of the six patients with available data. Treatments administered to the six hospitalized patients with available data included remdesivir for all six patients (4 patients at time of admission and 2 patients following admission when they developed an oxygen requirement) and dexamethasone for all three patients who developed an oxygen requirement. Of the three hospitalized patients who required supplemental oxygen, two patients recovered. The third patient, who had a prior history of lung cancer and Waldenstrom's macroglobulinemia recently treated with anti-CD20 therapy, progressed to respiratory failure and eventually died due to COVID-19. This same patient had been fully vaccinated. Overall, six (6.1%) of the 98 breakthrough patients developed chronic COVID-19, resulting in two COVID-19-related readmissions. As of March 31, 2023, a total of 15 (15.3%) AZD7442 recipients had experienced two breakthrough infections. The median time interval between the

Table 2. Comparison of AZD7442 dosing group as risk factors for SARS-CoV-2 breakthrough infection.

AZD7442 dosage	N	Total breakthrough cases	Total person-days	Median (IQR) days to COVID-19 diagnosis	Incidence rate per 1,000	Incidence rate ratio (95% CI)
Dose group 1: 1 dose 150-150 mg	149	35	21,834	92 (31-128)	1.60	ref.
Dose group 2: 2 doses 150-150 mg	292	35	50,222	138 (109-167)	0.70	0.43 (0.26-0.72)
Dose group 3: 1 dose 150-150 mg + 1 dose 300-300 mg	75	2	13,668	189.5 (181-198)	0.15	0.09 (0.01-0.36)
Dose group 4: 1 dose 300-300 mg	376	26	30,088	78 (43-97)	0.86	0.54 (0.32-0.92)

IQR: interquartile range; CI: confidence interval; COVID-19: coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table 3. Cox regression analysis of risk factors for SARS-CoV-2 breakthrough infection among high-risk hematologic malignancy patients stratified by dose of AZD7442 for pre-exposure prophylaxis.

Characteristic	Crude[a] Hazard ratio (95% CI)	*P*	*	Crude[a] Hazard ratio (95% CI)	*P*	*	Crude[a] Hazard ratio (95% CI)	*P*	*
	Group 1: 1 dose of 150-150 mg			Group 2: 2 doses of 150-150 mg			Group 4: 1 dose 300-300 mg		
Age in years: ≥65 *vs.* <65 (ref.)	0.65 (0.34-1.26)	0.202		0.56 (0.27-1.08)	0.082		0.59 (0.27-1.28)	0.183	
Sex: female *vs.* male (ref.)	0.79 (0.40-1.55)	0.484		0.64 (0.32-1.26)	0.195		0.67 (0.30-1.51)	0.334	
Laboratory									
Creatinine: ≥1.1 mg/dL *vs.* <1.1 mg/dL[c]	0.73 (0.33-1.61)	0.44		0.54 (0.22-1.30)	0.167		1.34 (0.60-3.00)	0.48	
Lymphocyte: ≥500 cell/mcL *vs.* <500 cell/mcL[d]	1.41 (0.50-4.00)	0.515		3.42 (0.47- 25.0)	0.225		0.65 (0.20-2.18)	0.489	
$CD3^+CD4^+$ (T4 helper) cells, blood: ≥200 cell/mcL *vs.* <200 cell/mcL[e]	0.70 (0.27-1.83)	0.464		6.81 (0.89-52.1)	0.065		0.27 (0.06-1.13)	0.073	
CD19: ≥50 cell/mcL *vs.* <50 cell/mcL[e]	2.62 (0.94-7.31)	0.065		1.05 (0.29-3.82)	0.94		1.37 (0.28-6.81)	0.699	
Neutrophils: ≥0.5 k/mcL *vs.*s <0.5 k/mcL[f]	0.63 (0.04-10.8)	0.753		0.95 (0.06-16.27)	0.974		0.21 (0.05-0.88)	0.032	*
Total IgG: ≥500 mg/dL *vs.* <500 mg/dL[c]	3.66 (0.71-18.94)	0.122		0.23 (0.01-9.39)	0.434		0.86 (0.02-35.9)	0.936	
Anti-spike SARS CoV-2 antibody levels (Abbot)									
Spike Ab: ≥1,000 AU/mL *vs.* <1,000 AU/mL[g]	1.75 (0.53-5.76)	0.361		0.72 (0.14-3.78)	0.695		1.36 (0.46-3.96)	0.577	
COVID-19 vaccination status									
≥3 vaccine doses: Yes *vs.* No[h]	1.03 (0.53-2.00)	0.928		1.14 (0.58-2.24)	0.706		1.20 (0.54-2.64)	0.655	
Comorbidities[i]									
At least one co-morbidity *vs.* no co-morbidity	0.81 (0.41-1.56)	0.532		0.81 (0.42-1.57)	0.523		0.76 (0.35-1.64)	0.488	
Atrial fibrillation: Yes *vs.* No	1.29 (0.45-3.65)	0.635		0.77 (0.24-2.51)	0.663		0.13 (0.01-2.25)	0.161	
Chronic lung disease: Yes *vs.* No	2.39 (0.73-7.82)	0.149		0.29 (0.02-4.85)	0.387		0.56 (0.03-9.56)	0.693	
Heart failure: Yes *vs.* No	1.04 (0.32-3.39)	0.953		0.57 (0.08-4.15)	0.577		0.84 (0.05-14.58)	0.903	
HIV: Yes *vs.* No	1.70 (0.10-28.8)	0.714		1.59 (0.10-27.2)	0.748		1.44 (0.08-25.0)	0.802	
Hypertension: Yes *vs.* No	0.95 (0.49-1.85)	0.879		0.65 (0.32-1.32)	0.232		1.15 (0.53-2.48)	0.731	
Diabetes: Yes *vs.* No	0.64 (0.19-2.07)	0.452		0.11 (0.01-1.90)	0.130		0.22 (0.01-3.78)	0.295	
Renal failure: Yes *vs.* No	1.00 (0.48-2.08)	0.998		0.78 (0.30-2.01)	0.605		1.38 (0.52-3.65)	0.522	
Systemic steroids: Yes *vs.* No[j]	1.28 (0.58-2.81)	0.547		0.54 (0.21-1.38)	0.196		1.27 (0.51-3.19)	0.608	
Anti-CD20 therapy: Yes *vs.* No[k]	0.68 (0.34-1.37)	0.277		1.67 (0.86-3.24)	0.13		0.51 (0.21-1.28)	0.153	
Cancer types									
Lymphoma	ref.	N/A		ref.	N/A		ref.	N/A	
Leukemia/myelodysplastic syndrome	1.64 (0.81-3.34)	0.173		0.96 (0.48-1.93)	0.901		1.35 (0.56-3.25)	0.506	
Myeloma/amyloidosis	0.72 (0.18-2.79)	0.63		0.33 (0.06-1.82)	0.203		1.17 (0.39-3.50)	0.785	
Other	1.86 (0.10-33.9)	0.677		N/A	N/A		N/A	N/A	
Chemotherapy: Yes *vs.* No[l]	0.74 (0.38-1.44)	0.374		0.82 (0.42-1.59)	0.549		0.81 (0.37-1.76)	0.589	
Relapse/refractory disease: Yes *vs.* No	1.34 (0.64-2.79)	0.434		1.01 (0.44-2.32)	0.974		0.74 (0.26-2.16)	0.586	
BMT CAR T: Yes *vs.* No[m]	1.33 (0.68-2.61)	0.412		0.94 (0.39-2.26)	0.885		1.46 (0.59-3.64)	0.417	
Body mass index[n]									
Healthy weight (18.5-24.9)	ref.	N/A		ref.	N/A		ref.	N/A	
Underweight (<18.5)	0.29 (0.02-5.31)	0.403		1.40 (0.18-11.04)	0.751		2.10 (0.27-16.4)	0.481	
Overweight (25.0-29.9)	0.96 (0.45-2.04)	0.905		2.08 (0.94-4.61)	0.07		0.86 (0.35-2.11)	0.734	
Obese (≥30.0)	0.71 (0.26-1.91)	0.5		1.01 (0.36-2.84)	0.984		0.93 (0.24-2.55)	0.884	

Ab: antibody; BMT: bone marrow transplant; CAR T; chimeric antigen receptor T-cell therapy; IgG: immunoglobulin G; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2. *Cox model with AZD7442 dosage as time-varying covariate. Cox proportional hazards regression. Forward selection with inclusion and selection criterion of $P<0.05$. [a]Clinical classifications were based on available data. [b]Odds ratios and *P* values were calculated from logistic regression applying Firth's correction, where appropriate. [c]Creatinine, IgG: Most recent values before first AZD7442 start date within the last 6 months. [d]Lymphocytes: Most recent 3 laboratory values within 12 months prior to first AZD7442 start date. All 3 counts must be <500 per microliter to be in the '<500' category. At least 1 count of value ≥500 per microliter is considered in the "≥500" category. One patient did not have 3 laboratory values prior to COVID-19 diagnosis. [e]CD4, CD19: most recent values before first AZD7442 start date within last year. [f]Neutrophils: most recent values before first AZD7442 start date within 1 month. [g]Spike antibody: most recent test value before first AZD7442 start date within 1 year. [h]Fully vaccinated (N): charts were manually reviewed for patients with no vaccine history in patient database. [i]Chronic conditions (atrial fibrillation, chronic lung disease [chronic obstructive pulmonary disease, bronchiectasis, asthma], heart failure, hypertension, human immunodeficiency virus (HIV), diabetes, renal failure) were based on ICD10 diagnosis codes within 12 months of the study period. [j]Systemic steroids includes patients who were on steroids within 30 days prior to first AZD7442 start date. Includes dexamethasone, methylprednisolone, hydrocortisone, prednisone. [k]Anti-CD-20 therapy (rituximab, obinutuzumab, tafasitamab, hyaluroinidase-rituximab, ofatumumab): given within the previous 12 months of AZD7442. [l]Chemotherapy during the study period. [m]BMT and CAR T-cell therapies combined with service dates within 1 year of the study period. [n]BMI: most recent value during past 12 months.

episodes was 157 days (range, 94-261 days). Notably, for 12 of 15 patients, the second infection occurred at a time when non-susceptible variants were dominant.

Most patients with breakthrough infection tested positive for SARS-CoV-2 using home antigen tests, and clinical samples were not accessible for WGS. Of the 33 patients with available RT-PCR swabs performed at MSKCC, 27 subvariants were successfully identified using WGS. Figure 1 shows days to breathrough infection in dose groups 1, 2, and 4 by expected subvariant based on sequencing results when available or dominant circulating strain at the time of illness.

Discussion

In our study cohort of highly vaccinated hematologic malignancy patients who received AZD7442 as pre-exposure prophylaxis against SARS-CoV-2 infection in the era of Omicron, 10.9% of recipients had breakthrough infection. Of those with breakthrough infection, the majority received early outpatient treatment (82%) and eventually eight (8.2%) required hospitalization for management of COVID-19, with a single instance of severe COVID-19 and death. Patients who received a repeat dose of AZD7442 or a higher first-time dose of AZD7442 had a lower incidence of breakthrough infection. Notably, no host factors or treatment-related factors predicted the risk of breakthrough infection in our study cohort.

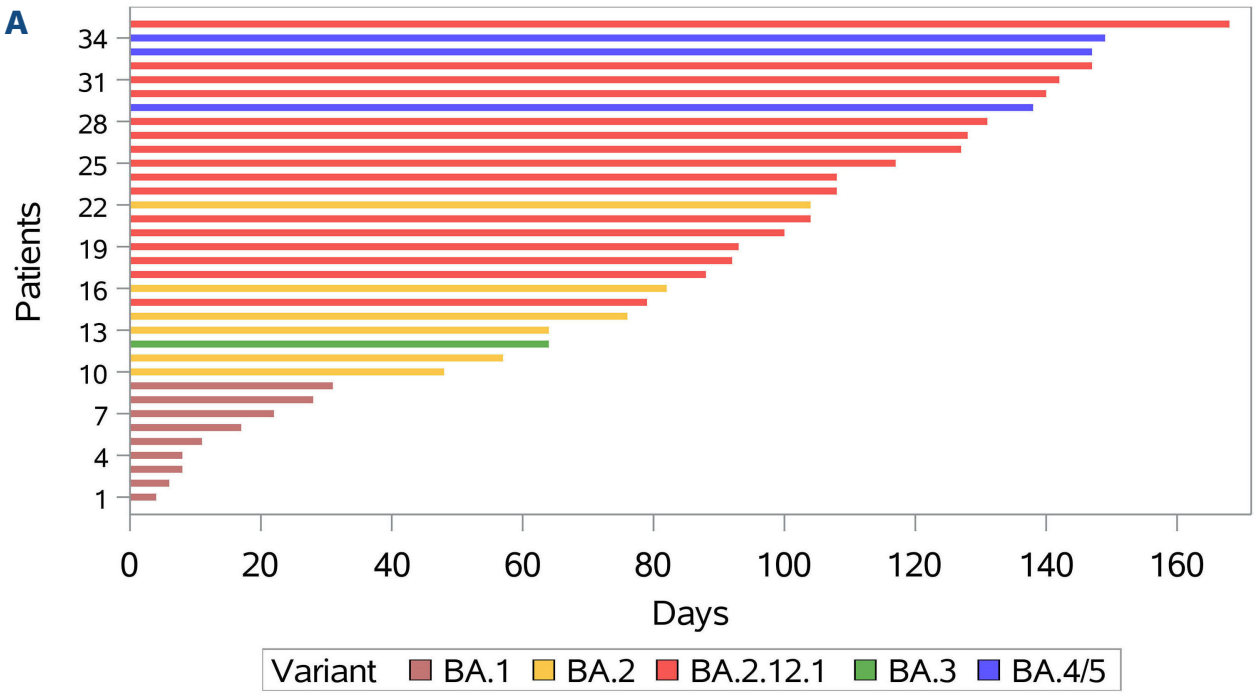
The critical PROVENT trial demonstrated an 83% relative risk reduction in developing symptomatic COVID-19 among vaccine-naïve patients who received AZD7442 for prevention compared to placebo at a median follow-up of 6 months.[12] However, the study population only consisted of 7.2% cancer patients, and it only evaluated a single 150-mg dose each of tixagevimab and cilgavimab given as two consecutive intramuscular injections. The post-EUA experience marked by rapid evolution of Omicron subvariants with lower neutralizing activity raised concerns about decreased efficacy among immunocompromised patients. For example, an *in vitro* neutralization study by Boschi *et al*. demonstrated that the combination of AZD7442 was 233 times less active against B.1.1.529 than against the Delta variant.[22] Stuver *et al*. found that AZD7442 failed to achieve meaningful neutralization of Omicron among 52 patients with hematologic malignancies who were treated with a single 150 mg dose each of tixagevimab and cilgavimab.[23] Although the results were heterogenous, neutralization activity improved with either a second dose of 150 mg each of tixagevimab and cilgavimab or in those who received 300 mg each of tixagevimab and cilgavimab, supporting the revised FDA dosing regimen.

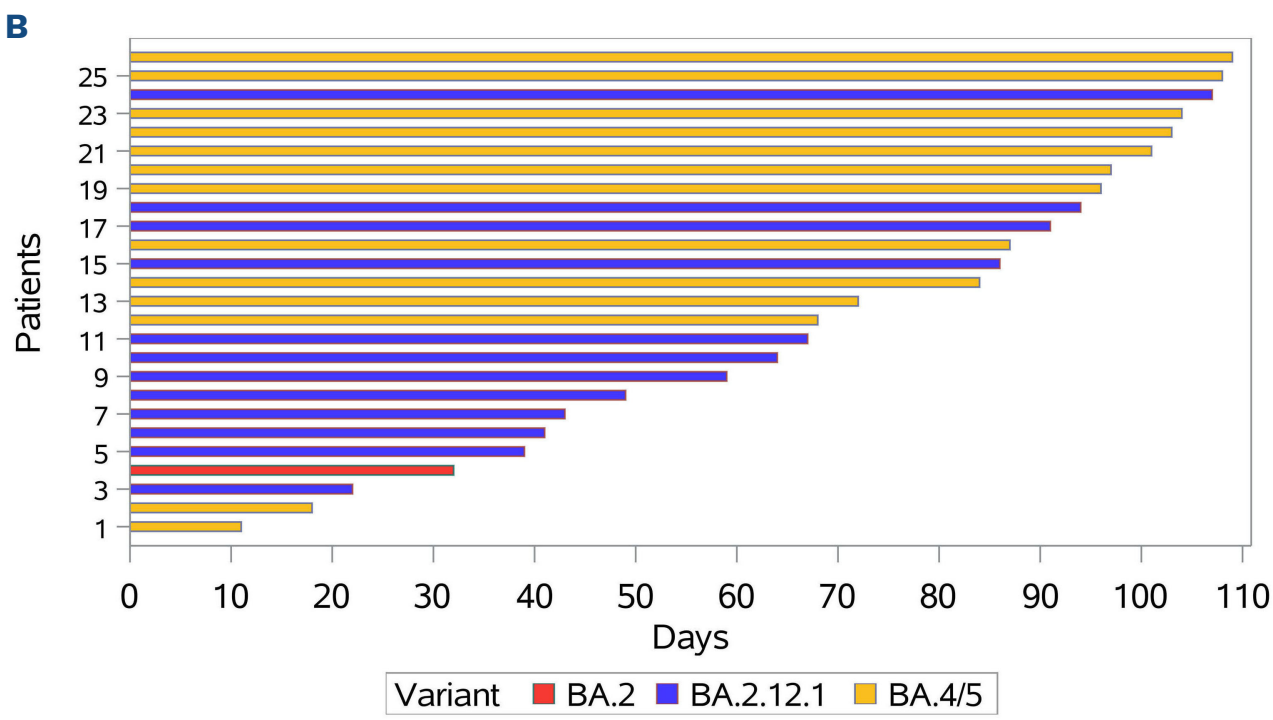
There are likely multiple factors accounting for the vary-

Table 4. Clinical characteristics and outcomes for 98 patients with breakthrough infection from SARS-CoV-2 after receiving AZD7442 for pre-exposure prophylaxis.

Characteristic	N (%)[a]
Age in years, median (IQR)	65 (53-74)
Sex, male	61 (62.2)
Unvaccinated	6 (6.1)
Required hospitalization	8 (8.2)
Symptoms at hospitalization (N=6)	
Fever	6 (100.0)
Dyspnea	3 (50.0)
Cough	4 (66.7)
Nasal congestion	4 (66.7)
Poor oral intake	4 (66.7)
Chest pain	2 (33.3)
Fatigue	4 (66.7)
CT chest findings (N=2)	
Bilateral consolidative opacities	0 (0)
Bilateral patchy ground-glass opacities	1 (50)
Clear lungs	1 (50)
CXR findings (N=6)	
Unilateral opacities	1 (16.7)
Bilateral opacities	1 (16.7)
Clear lungs	4 (66.7)
Oxygen requirement (N=6)	
No oxygen requirement or <24 hours	3 (50.0)
Nasal cannula >24 hours	2 (33.3)
High flow oxygen	1 (16.7)
Mechanical ventilation	0 (0)
COVID-19 severity[b] (N=6)	
Mild	3 (50.0)
Moderate	2 (33.3)
Severe/critical	1 (16.7)
COVID-19 treatment (N=98)	
Any COVID-19 treatment	81 (82.6)
Nirmatrelvir-ritonavir	31 (31.6)
Remdesivir	8 (8.2)
Dexamethasone	4 (4.1)
Bebtelovimab	40 (40.8)
Sotrovimab	7 (7.1)
COVID-19 outcome (N=98)	
COVID-19-related death[c]	1 (1.)
COVID-19-related readmission	2 (2.0)
Chronic infection[d]	6 (6.1)

COVID-19: coronavirus disease 2019; CT: computed tomography; CXR: chest radiograph; IQR: interquartile range. [a]Patients can be in >1 category. [b]COVID-19 severity based on maximum oxygen requirement through admission. Mild infections remain on room air or required nasal canula for <24 hours; moderate infections required nasal canula >24 hours; severe/critical infections required high flow oxygen or intubation. [c]COVID-19-related deaths are based on review of electronic medical records and clinical judgement of patient presentation/illness in relation to patients' primary disease. [d]Chronic infection from COVID-19 is defined as patients who had progressive or recurrent COVID-19-related symptoms in the absence of an alternative explanation and with or without evidence of viral persistence.





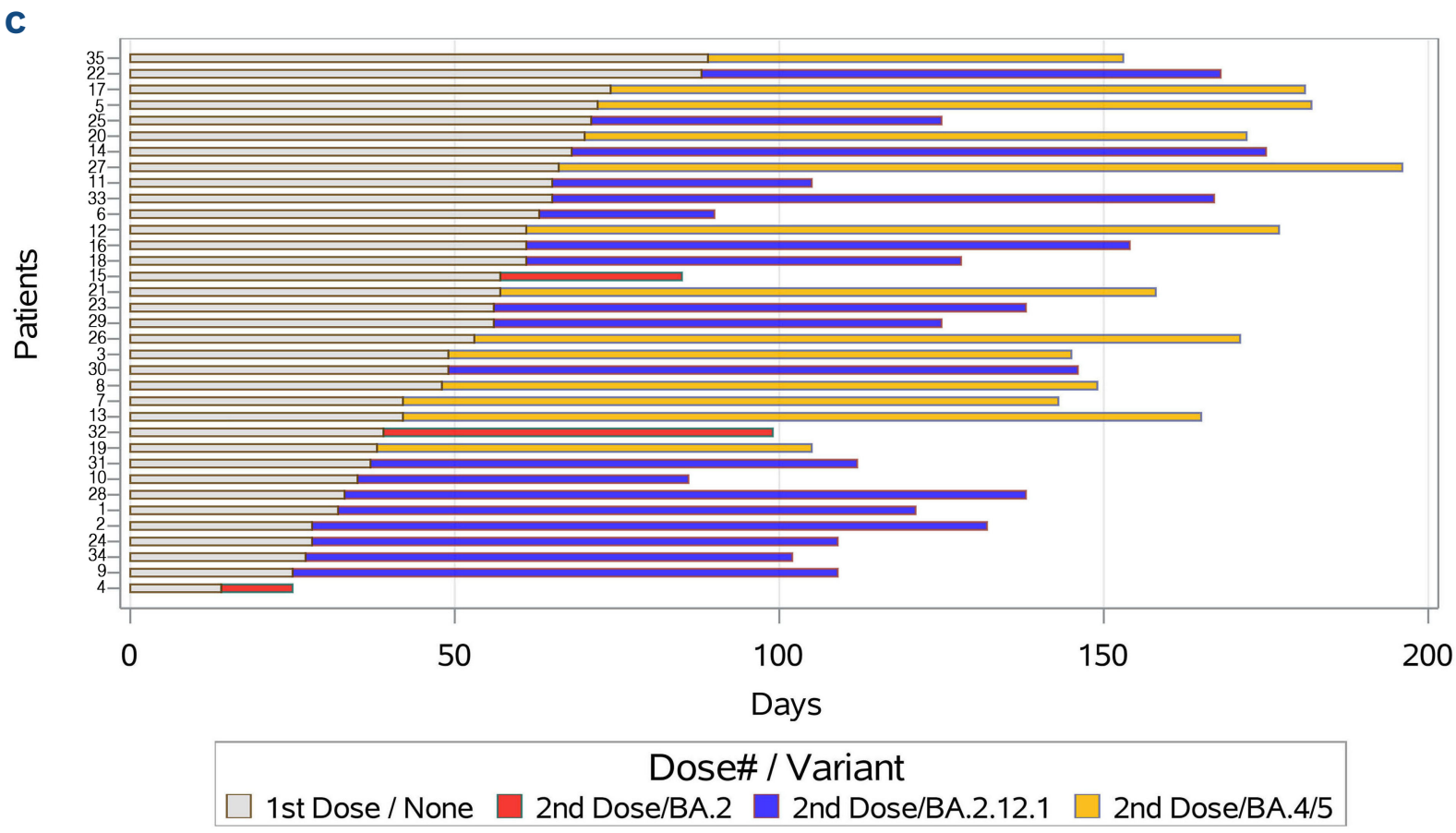


Figure 1. Days to breakthrough infection in dose groups 1, 2, and 4 by Omicron subvariant as predicted by date of positivity or whole genome sequencing, when available. (A) Dose group 1: single 150-150 mg dose of AZD7442. (B) Dose group 2: two 150-150 mg doses of AZD7442. (C) Dose group 4: single 300-300 mg dose of AZD7442.

ing efficacy of AZD7442 observed across published studies. First, vaccination rates of AZD7442 recipients have varied significantly between studies. The critical PROVENT trial leading to the FDA's EUA for AZD7442 was conducted in unvaccinated patients.[12] However, post-marketing clinical studies such as those by Kertes *et al*. and Najjar-Debbiny *et al*., which demonstrated reduced efficacy of AZD7442 compared to PROVENT, had a majority of patients who received at least one dose of vaccine against SARS-CoV-2.[24,25] A second major factor contributing to differences in AZD7442 efficacy between studies is the rapid evolution of SARS-CoV-2 variants with critical receptor binding domain mutations that reduce antibody binding. While PROVENT was conducted prior to the emergence of Omicron, subsequent studies have been conducted against different Omicron sublineages that have demonstrated wide variability in susceptibility to AZD7442.[10] For example, in a large cohort study of 1,112 patients with heterogenous immunocompromising conditions, Nguyen *et al*. reported breakthrough infection in 4.4% of patients treated with 150-150 mg of AZD7442 during regional BA.1 and BA.2 predominance while Jondreville *et al*. observed that 22 of 161 (14%) of adult allogenic hematopoietic stem cell transplant recipients treated with 150-150 mg of AZD7442 developed breakthrough infection during the Omicron wave (sublineages not specified).[26,27] The difference in infection rate between studies by Nguyen *et al*. and Jondreville *et al*. also highlights how differences in patient population may contribute to variability in AZD7442 efficacy.

Another major factor contributing to differences in AZD7442 efficacy between studies is the variation in dosing regimens studied. In a study of 203 patients with hematologic malignancies, 97% of whom received the 300-300 mg dose of AZD7442 and nearly all of whom had received at least one dose of mRNA vaccine, Ocon *et al*. found that 19 (9.3%) patients developed breakthrough infection, a finding that is comparable to the breakthrough rate in our study.[28] Multiple other studies have included patient cohorts treated with both 150-150 mg and/or 300-300 mg of AZD7442 with variability in observed efficacy of AZD7442 likely related to differences in patient population, vaccine history, dose, and circulating subvariants.[29-33]

There are several limitations to our study. First, and most importantly, the small sample sizes of SARS-CoV-2 breakthrough infections and missing laboratory parameters in each of the dose groups did not allow for robust analyses. Although we had a consistent mechanism for capturing self-administered rapid antigen tests, it is possible that we missed breakthrough infections and have underestimated the overall rate of mild infections. Second, the lack of a AZD7442 naïve comparator arm precludes more definitive discrimination of AZD7442 effectiveness. While our report is the most extensive cohort experience of high-risk hematologic malignancy patients, especially regarding measurement of dose-specific incidence of breakthrough infection, the findings do not extend to other immunocompromised patient populations. In contrast to published trials that were mostly conducted in those with elevated but non-cancer-related risk of SARS-CoV-2 infection, our study cohort overwhelmingly represents actively treated and vaccinated hematologic malignancy patients. Finally, the impact of AZD7442 alone on clinical outcomes (e.g., hospitalization, mortality) cannot be made at this time in the era of early effective anti-SARS-CoV-2 therapies. As newly circulating variants are non-susceptible to AZD7442, the results of our study cannot be generalized to the post-Omicron, mab-resistant era.[34, 35]

In summary, high-risk hematologic malignancy patients who received AZD7442 for pre-exposure prophylaxis against SARS-CoV-2 had a breakthrough infection rate of 11%, most infections were mild, with minimal risk of hospitalization and severe disease. In addition, our dose-specific analysis of breakthrough incidence rates shows that patients who received a second, or a higher initial dose of AZD7442, as per revised FDA guidance had better protection against breakthrough infection, providing the clinical evidence to support the FDA's dosing modification based on *in vitro* neutralization activity against circulating variants. Most importantly, our study's low incidence of severe outcomes underscores the swift and valuable therapeutic advancements that have been made for the prevention and early treatment of high-risk patients who cannot solely rely on vaccine-induced protection to reduce SARS CoV-2 related adverse outcomes.

Disclosures

EVR has received consulting fees from Replimune. NEB has received research grants from GenMark Diagnostics and ArcBio/Canta and is on the advisory board at Bio-Rad Molecular, Agena Diagnostics, and ArcBio/Canta. SKS has an investigator-initiated grant from Merck. MK has acted as a consultant for Regeneron and has received speaker fees for WebMD/Medscape.

Contributions

All authors critically reviewed and contributed to the writing of the manuscript, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work. JL, JY, MK, and SKS were responsible for the conception and design of the study, interpretation of the data, and preparation of the manuscript. MK and SKS managed the study. JY, SNS, JL, JF, CAT, NC and SKS acquired the data. JY and NEB analyzed the data. JY performed statistical analysis. JY and JL produced the figures and tables. NEB analyzed laboratory samples; and all authors reviewed the final draft.

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Data-sharing statement

The authors are committed to the dissemination of data. However, the raw data are not available for sharing as no specific consent for this purpose was available.

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